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**RELATED PCT APPLICATION NUMBER:** *PCT/US04/23726*

Certified by

Jon W Dudas

Acting Under Secretary of Commerce
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Sir:

Transmitted herewith for filing is a **PROVISIONAL** Patent Application under 37 C.F.R. §1.53(c) of:

| | Attorney Dkt. No. 40394-P3012 | | Type a (+) in this box → | + |
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For: **p-38 KINASE INHIBITORS**

**PROVISIONAL APPLICATION**
**DOCKET NO. 40394-P3012**
**Lang *et al.***

The subject matter in this application was not made under contract with an agency of the United States Government.

Enclosed are:

[X] The specification containing 80 pages including claims and abstract.

Status as Small Entity
[X] is claimed, reducing Filing Fee by one-half to $80.00
[ ] is not claimed.

[X] A check in the amount of $80.00 to cover the filing fee.

[ ] Charge $___ to Deposit Account No. 50-1213.

[X] The Commissioner is hereby authorized to charge any fees, including any due herein, that may be required in this application under during its entire pendency, or credit any overpayment, to Deposit Account No. 50-1213. If proper payment is not enclosed, such as a check in the wrong amount, unsigned, post-dated, otherwise improper or informal, or absent, the Commissioner is authorized to charge the unpaid amount or total amount due to Deposit Account No. 50-1213 during the entire pendency of this application. This sheet is filed in triplicate.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
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# p-38 KINASE INHIBITORS

## Field of the Invention

The present invention relates to compounds which have cytokine inhibitory activity. The present invention also relates to the use of aryl and heteroaryl compounds for treating conditions associated with p38α and β kinases and for treating p38 kinase-associated conditions.

## Background of the Invention

A large number of cytokines participate in the inflammatory response, including IL-1, IL6, IL-8 and TNF-α. Overproduction of cytokines such as IL-1 and TNF-α are implicated in a wide variety of diseases, including inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, endotoxin shock, osteoporosis, Alzheimer's disease, and congestive heart failure, among others [Henry *et al.*, Drugs Fut., 24:1345-1354 (1999); Salituro *et al.*, Curr. Med. Chem., 6:807-823 (1999)]. Evidence in human patients indicates that protein antagonists of cytokines are effective in treating chronic inflammatory diseases, such as, for example, monoclonal antibody to TNF-α (Remicade) [Rankin *et al.*, Br. J. Rheumatol., 34:334-342 (1995)], and soluble TNF-α receptor-Fc fusion protein (Etanercept) [Moreland *et al.*, 25 Ann. Intern. Med., 130:478-486 (1999)].

The biosynthesis of TNF-α occurs in many cell types in response to an external stimulus, such as, for example, a mitogen, an infectious organism, or trauma. Important mediators of TNF-α production are the mitogen-activated protein (MAP) kinases, and in particular, p38 kinases. These kinases are activated in response to various stress stimuli, including but not limited to proinflammatory cytokines, endotoxin, ultraviolet light, and osmotic shock. Activation of p38 requires dual phosphorylation by upstream MAP kinase kinases (MKK3 and MKK6) on threonine and tyrosine within a Thr-Gly-Tyr motif characteristic of p38 isozymes.

There are four known isoforms of p38, i.e., p38α, p38β, p38γ, and p38δ. The α and β

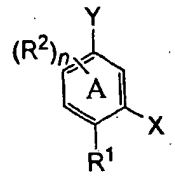
isoforms are expressed in inflammatory cells and are key modulators of TNF-α production. Inhibiting the p38α and β enzymes in cells results in reduced levels of TNF-α expression. Also, administering inhibitors of p38α and β in animal models of inflammatory disease has proven that such inhibitors are effective in treating those diseases. Accordingly, the p38 enzymes serve an important role in inflammatory processes mediated by IL-1 and TNF-α. Compounds that reportedly inhibit p38 kinase and cytokines such as IL-1 and TNF-α for use in treating inflammatory diseases are disclosed in US Pats. Nos. 6,277,989 and 6,130,235 to Scios, Inc; US Pats. Nos. 6,147,080 and 5,945,418 to Vertex Pharmaceuticals Inc; US Pats Nos. 6,251,914, 5,977,103 and 5,658,903 to Smith-Kline Beecham Corp.; US Pats. Nos. 5,932,576 and 6,087,496 to G.D. Searle & Co.; WO 00/56738 and WO 01/27089 to Astra Zeneca; WO 01/34605 to Johnson & Johnson; WO 00/12497 (quinazoline derivatives as p38 kinase inhibitors); WO 00/56738 (pyridine and pyrimidine derivatives for the same purpose); WO 00/12497 (discusses the relationship between p38 kinase inhibitors); and WO 00/12074 (piperazine and piperidine compounds useful as p38 inhibitors).

Pyrrolotriazine compounds useful as tyrosine kinase inhibitors are disclosed in US patent application Serial No. 09/573,829 filed May 18, 2000, assigned to Bristol-Myers Squibb. In addition, pyrrolotriazine kinase inhibitors are disclosed in WO 02/40486, assigned to Bristol-Myers Squibb. Other applications disclosing p38 kinase inhibitors include: WO 03/032970, WO 03/033482, WO03/032971, WO 03/032986, WO 03/032980, WO 03/032987, WO 03/033483, WO 03/033457 and WO 03/032972 are incorporated into this application. Each of the patent applications, patents, and publications referred to herein is incorporated herein by reference.

## Summary of the Invention

The present invention provides methods of treating conditions associated with p38 kinase activity, comprising administering to a patient in need thereof certain aryl and heteroaryl compounds. The invention further provides select heteroaryl amides useful as kinase inhibitors, particularly kinases p38α and β.

The present invention relates to compound I of the formula:



I

or a pharmaceutically acceptable salt and or hydrate thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

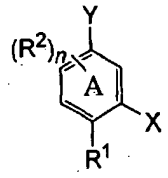
This invention also relates to a pharmaceutical composition that is comprised of a compound of formula I as defined above in combination with a pharmaceutically acceptable carrier.

Also included in the invention is a method of treating cytokine mediated disease in a mammal, comprising administering to a mammalian patient, in need of such treatment, an amount of compound of formula I which is effective to treat the cytokine mediated disease.

Also provided are methods of inhibiting p38 kinases, including p38α and p38β kinases, using the compounds and compositions provided herein. Further provided are methods of mediating cytokine response using the compounds and compositions provided herein.

## Detailed Description of the Invention

The present invention relates to compounds represented by formula (I):

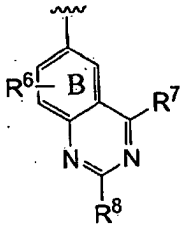


I

or a pharmaceutically acceptable salt or hydrate thereof,

wherein:

X is



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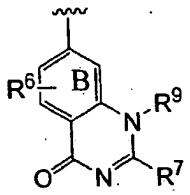

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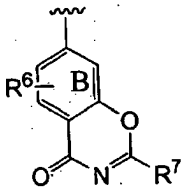

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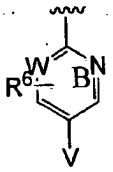

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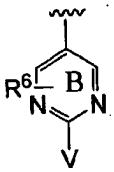

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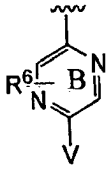

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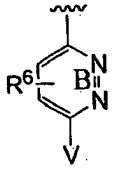

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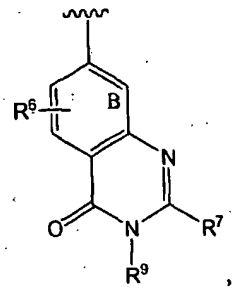


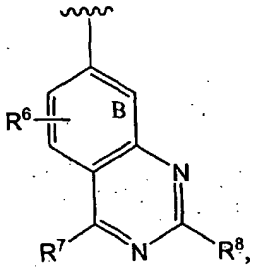


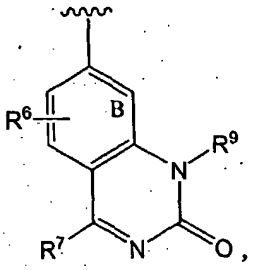


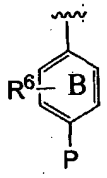


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$R^1$ is selected from hydrogen, methyl, halogen, hydroxyl, lower alkyl, lower cycloalkyl, alkynyl, trifluoromethyl, methoxy, trifluoromethoxy, cyano, $-NH_2$, $-NR^4R^5$ and $-OR^4$;

$R^2$ is attached to any available carbon atom of the phenyl ring A and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NMe_2$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-aryl-$R^4$, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

$R^3$ is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted

heterocycle;

n is 0 or 1;

t is selected from 0, 1, 2 and 3;

e is selected from 0, 1, 2 and 3;

W is CH or N;

V is –M-$R^{10}$ or $R^{14}$;

M is –C(=O)$NR^4$-,-$NR^4$(C=O)-, -$NR^4$(C=O)$NR^4$-, -$NR^4SO_2$-, -C(=O)-;

$R^{14}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

P is –Q-$R^{10}$ or $R^{15}$;

Q is -$NR^4$ (C=O)-, -$NR^4$ (C=O)$NR^4$-, -$SO_2NR^4$-, -$NR^4SO_2$-, -C(=O)-;

$R^{15}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

Y is –L-$R^3$ or $R^{11}$;

L is –C(=O)NH-,-NH(C=O)-, -$SO_2$NH-, -$NHSO_2$-, -C(=O)-;

$R^{11}$ is an optionally substituted 5-membered heteroaryl;

$R^4$ and $R^5$ are each selected independently from hydrogen, lower alkyl and lower cycloalkyl;

$R^6$ is attached to any available carbon atom of the phenyl ring B and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, -$NH_2$, -$NMe_2$; -S(=O)alkyl, -S(=O)aryl, -$NHSO_2$-aryl-$R^4$, -$NHSO_2$alkyl, -$CO_2R^4$, -$CONH_2$, -$SO_3H$, -S(O)alkyl, -S(O)aryl, -$SO_2NHR^4$, -NHC(=O)$R^4$, and –NHC(=O)$NHR^4$;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, substituted

alkyl, aryl, cycloalkyl;

$R^9$ is hydrogen, alkyl, substituted alkyl, cycloalkyl;

$R^{10}$ is alkyl, substituted alkyl, aryl, and $-(CH_2)_t-D-(CH_2)_e-R^{13}$;

D is selected from a bond, an optionally substituted heterocycle, an optionally substituted aryl, -O-, -S-, -(C=O)-, $-NR^4(C=O)-$, $-(C=O)NR^4-$, -S(O)-, $SO_2NR^4-$, $SO_2-$, and $-NR^4-$

$R^{12}$ is selected from $R^{10}$, $NO_2$, CN, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NMe_2$; $-S(=O)$alkyl, -S(=O)aryl, $-NHSO_2$-aryl-$R^4$, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

$R^{13}$ is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring.

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

As used herein, p38α refers to the enzyme disclosed in Han J, Richter B, Li Z, Kravchenko V, Ulevitch RJ. Molecular cloning of human p38 MAP kinase. Biochim Biophys Acta. 1995 ;1265(2-3):224-7. As used herein, p38β refers to the enzyme disclosed in Jiang Y, Chen C, Li Z, Guo W, Gegner JA, Lin S, Han J. Characterization of the structure and function of a new mitogen-activated protein kinase (p38beta).J Biol Chem. 1996 Jul 26;271(30):17920-6. As used herein, p38γ refers to the enzyme disclosed in Li, Z.; Jiang, Y.; Ulevitch, R. J.; Han, J. : The primary structure of p38-gamma: a new member of p38 group of MAP kinases. *Biochem. Biophys. Res. Commun.* 228: 334-340, 1996. As used herein, p38δ refers to the enzyme disclosed in

Molecular Cloning and Characterization of a Novel p38 Mitogen-activated Protein Kinase Xuhong Sunny Wang, Katrina Diener, Carl L. Manthey , Shen-wu Wang , Bradley Rosenzweig , Jeffrey Bray , John Delaney, Craig N. Cole, Po-Ying Chan-Hui , Nathan Mantlo , Henri S. Lichenstein , Mark Zukowski and Zhengbin Yao.

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, in another embodiment 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms. When a subscript is used with reference to an alkyl or other group, the subscript refers to the number of carbon atoms that the group may contain. The term "$C_{1_4}$alkyl" includes a bond and alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by one to four substituents, in another embodiment, one, two or three substituents, selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, *e.g.* $SO_2NH_2$, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, *e.g.* $CONH_2$, substituted carbamyl e.g. CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where the substituent on the alkyl is further substituted, it will be with alkyl, alkoxy, aryl, or aralkyl.

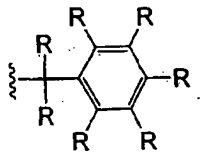
When the term alkyl is used in connection with another group, as in heterocycloalkyl or cycloalkylalkyl, this means the identified group is bonded directly through an alkyl group which may be branched or straight chain. In the case of substituents, as in "substituted cycloalkylalkyl," the alkyl portion of the group may, besides being branched or straight chain, be substituted as recited above for substituted alkyl groups and/or the connected group may be substituted as recited herein for that group.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups. When the aryl is substituted, each ring of the aryl may be substituted.

The term "substituted aryl" refers to an aryl group substituted by one to four substituents, in another embodiment, one, two or three substituents, selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyan, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, and aryloxy. The substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl, wherein the alkyl group may be branched or straight chain. In the case of a "substituted aralkyl," the alkyl portion of the group may, besides being branched or straight chain, be substituted as recited above for substituted alkyl groups and/or the aryl portion may be substituted as recited for substituted aryl. Thus, the

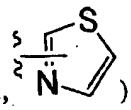



term "optionally substituted benzyl" refers to the group wherein each R group may be hydrogen or may also be selected from alkyl, halogen, cyano, nitro, amino, hydroxy, allcoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy, and other groups recited above. In one embodiment, at least two of these "R" groups are hydrogen. In another embodiment, at least five of the "R" groups are hydrogen.

The term "heteroaryl" refers to an aromatic group for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom and at least one carbon atom containing ring. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms, provided that the total number of

heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring.

A "substituted heteroaryl" has one to four substituents on any one or more of the rings pomprising the heteraryl group. The substituents may be selected from those 30 recited below for heterocycle groups.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl (i. e.,  ) thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzopuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, in one embodiment 2 to 15 carbon atoms, in another embodiment 2 to 8 carbon atoms, having one to four double bonds, in another embodiment one or two double bonds.

The term "substituted alkenyl" refers to an alkenyl group substituted by one to two substituents selected from halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, diallcylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl,

sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino, and substituted and unsubstituted heterocycles, including indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, in one embodiment 2 to 15 carbon atoms, in another embodiment 2 to 8 carbon atoms, having one to four triple bonds in another embodiment one or two triple bonds.

The term "substituted alkynyl" refers to an alkynyl group substituted by a substituent selected from halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, allcylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, damantly and substituted or unsubstituted heterocyclo, e.g. imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "cycloalkyl" refers to a saturated or partially unsaturated nonaromatic cyclic hydrocarbon ring system, in one embodiment containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated $C_3$-$C_7$ carbocylic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cycloctyl, cyclodecyl, cyclododecyl, and damantly. A "substituted cycloalkyl" is substituted with one or more alkyl or substituted alkyl groups as described above, or one or more groups described above as alkyl substituents. The expression "lower cycloalkyl" refers to an unsubstituted saturated or unsaturated nonaromatic cyclic hydrocarbon ring system containing 3 to 5 carbon atoms.

The terms "heterocycle", "heterocyclic" and "heterocyclo" each refer to a fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered mono cyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom - containing ring. Thus, the term "heterocycle" includes heteroaryl groups as described above. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen or sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include 2,3-dihydro-2-oxo-1H-indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo [2,3 -c]pyridinyl, furo [3, 1 -b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofiuyl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Also included are smaller heterocycles, such as epoxides and aziridines.

A "substituted heterocycle" will be substituted with one or more alkyl or aralkyl groups as described above, and/or one or more groups described above as alkyl substituents.

Unless otherwise indicated, when reference is made to a specifically-named heterocyclo or heteroaryl, the reference is intended to include those systems having the maximum number of non-cumulative double bonds or less than that maximum number of double bonds. Thus, for example, the term "isoquinoline" refers to isoquinoline and tetrahydroisoquinoline. The term "diazepine" refers to a heterocyclo ring having at least one seven atom ring with two nitrogen atoms in the seven membered ring,

including a fully saturated or unsaturated diazepine.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

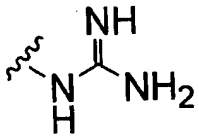
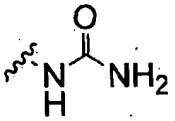
The term "haloalkyl" means an alkyl having one or more halo substituents

The term "fluoromethyl" means a methyl group substituted by one, two, or three fluoro atoms, i.e., $CH_2F$, $CHF_2$ and $CF_3$. The term "fluoroalkyl" means an alkyl group having from one to five fluoro atoms, such as pentafluoroethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes -$OCF_3$.zzz

The term "carbocyclic" means a saturated or unsaturated unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

Definitions for the various other groups that are recited above in connection with substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, substituted heterocycle, substituted cycloalkyl, and so forth, are as follows: alkoxy is -$OR^a$, alkanoyl is -$C(=O)R^a$, aryloxy is -OAr, alkanoyloxy is -$OC(=O)R^a$, amino is -$NH_2$, alkylamino is $NHR^a$, arylamino is -NHAr, aralkylamino is NH-$R^b$-Ar, disubstituted amine or dialkylamino is $NR^cR^d$, alkanoylamino is -NH-$C(=O)R^a$, aroylamino is -NH-C(=O)Ar, aralkanoylamino is NH-$C(=O)R^b$-Ar, thiol is -SH, alkylthio is -$SR^a$, arylthio is -SAr, aralkylthio is -S-$R^b$-Ar, alkylthiono is -$S(=O)R^a$, arylthiono is -S(=O)Ar, aralkylthiono is -$S(=O)R^b$-Ar, alkylsulfonyl is -$SO_{(q)}R^a$, arylsulfonyl is -$SO_{(q)}$Ar, arylsulfonylamine is -$NHSO_{(q)}$Ar, alkylsulfonylamine is $NHSO_2R^a$, aralkylsulfonyl is -$SO_{(q)}R^b$Ar, sulfonamido is -$SO_2NH_2$, nitro is -$NO_2$, carboxy is -$CO_2H$, carbamyl is –$CONH_2$, substituted carbamyl is -$C(=O)NHR^c$ or -$C(=O)NR^cR^d$, alkoxycarbonyl is -$C(=O)OR^a$, carboxyalkyl is -$R^b$-$CO_2H$, , sulfonic acid is -$SO_3H$, arylsulfonylamine is -$NHSO_{(q)}$Ar, guanidino is  and ureido is  , wherein $R^a$ is alkyl as defined above, $R^b$ is alkylene

as defined above, $R^c$ and $R^d$ are selected from alkyl, aryl, and aralkyl, Ar is an aryl as defined above, and q is 2 or 3.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.

The compounds of Formula (I, II, III & IV) may form salts which are also within the scope of this invention. In one embodiment, the sats are pharmaceutically acceptable (i.e. non-toxic, physiologically acceptable) salts, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention.

The compounds of Formula (I) may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts can be formed as known to those skilled in the art.

The compounds for Formula (I) may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, oxalic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts can be formed as known to those skilled in the art.

Salt forms of the compounds may be advantageous for improving the compound dissolution rate and oral bioavailability.

In addition, zwitterions ("inner salts") may be formed.

All stereoisomers of the compounds of the this invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

Compounds of the Formula (I) may also have prodrug forms. Any compound

that will be converted *in vivo* to provide the bioactive agent (i.e., the compound for formula I) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) **Design of Prodrugs,** edited by H. Bundgaard, (Elsevier, 1985) and **Methods in Enzymology,** Vol.42, p. 309-396, edited by K. Widder, et al. (Acamedic Press, 1985);

b) **A Textbook of Drug Design and Development,** edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113-191 (1991); and

c) H. Bundgaard, **Advanced Drug Delivery Reviews,** 8, 1-38 (1992),

each of which is incorporated herein by reference.

It should further be understood that solvates (e.g., hydrates) of the compounds of Formula (I) are also with the scope of the present invention. Methods of solvation are generally known in the art.

## Utility

The compounds of the invention are selective inhibitors of p38 kinase activity, and in particular, isoforms p38α and p38β. Accordingly, compounds of formula (I) have utility in treating conditions associated with p38 kinase activity. Such conditions include diseases in which cytokine levels are modulated as a consequence of intracellular signaling *via* p38, and in particular, diseases that are associated with an overproduction of cytokines IL-l, IL-4, IL-8, and TNF-α. As used herein, the terms "treating" or "treatment" encompass either or both responsive and prophylaxis measures, e.g., designed to inhibit or delay the onset of the disease or disorder, achieve a full or partial reduction of the symptoms or disease state, and/or to alleviate, ameliorate, lessen, or cure the disease or disorder and/or its symptoms. When reference is made herein to inhibition of "p-38α/β kinase," this means that either p38α and/or p38β kinase are inhibited. Thus, reference to an $IC_{50}$ value for inhibiting p-38α/β kinase means that the compound has such effectiveness for inhibiting at least one of, or both of, p38α and p38β kinases.

In view of their activity as inhibitors of p38α/β kinase, compounds of Formula (I)

are useful in treating p-38 associated conditions including, but not limited to, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, angiogenic disorders, infectious diseases, neurodegenerative diseases, and viral diseases.

More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosis, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β-cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, meloid formation, scar tissue formation, ulcerative colitis, pyresis, influenza, osteoporosis, osteoarthritis and multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders including solid tumors, ocular neovasculization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS, SARS, ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hyposia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin induced platelet aggregation, endotoxemia and/or toxic shock syndrome, and conditions associated with prostaglandin endoperoxidase synthase-2.

In addition, p38 inhibitors of this invention inhibit the expression of inducible

pro-inflammatory proteins such as prostaglandin endoperoxide synthase-2 (PGHS-2),also referred to as cyclooxygenase-2 (COX-2). Accordingly, additional p38--associated conditions include edema, analgesia, fever and pain, such as neuromuscular pain, headache, pain caused by cancer, dental pain and arthritis pain. The inventive compounds also may be used to treat veterinary viral infections, such as lentivirus infections, including, but not limited to equine infectious anemia virus; or retro virus infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus. When the terms "p38-associated condition" or "p38-associated disease or disorder" are used herein, each is intended to encompass all of the conditions identified above as if repeated at length, as well as any other condition that is affected by p38 kinase activity.

The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof an effective amount of at least one compound of Formula (I) or a salt thereof. The methods of treating p38 kinase--associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, CSAIDs, 4-substituted imidazo [1,2A]quinoxalines as disclosed in US Pat. No. 4,200,750 and in S. Ceccarelli *et al, "Imidazo[l, 2-a]quinoxalin-4-amines: A Novel Class of Nonxanthine $A_1$ Adenosine Receptor Antagonists,"* European Journal of Medicinal Chemistry Vol. 33, (1998), at pp. 943-955; Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathioprine and cyclophosphamide; TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one

of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds.

The present invention also provides pharmaceutical compositions capable of treating p38-kinase-associated conditions, including TNF-α, IL-1, and/or IL-8 mediated conditions, as described above. The inventive compositions may contain other therapeutic agents as described above and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (e.g., excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The compounds of Formula (I) may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systemic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques (e.g., as sterile injectable aq. or non-aq. solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps. Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid

or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by, sublingual and/or buccal administration, e.g., with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (e.g., GANTREZ®); and agents to control release such as polyacrylic copolymer (e.g., CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage

amounts for a mammal of from about 0.05 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. In one embodiment, the subjects for treatment include animals, in another embodiment mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used herein, this term is intended to include all subjects, including mammalian species, that are affected by mediation of p38 enzyme levels.

## Abbreviations

Ph = phenyl

Bz = benzyl

t-Bu = tertiary butyl

Me = methyl

Et = ethyl

Pr = propyl

Iso-P = isopropyl

MeOH = methanol

EtOH = ethanol

EtOAc = ethyl acetate

Boc = tert-butyloxycarbonyl

CBZ = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl

DCM = dichloromethane

DCE = 1,2-dichloroethane

DMF = dimethyl formamide

DMSO = dimethyl sulfoxide

TFA = trifluoroacetic acid

THF = tetrahydrofuran

HATU = *O*-(7-Azabenzotriazol-1-yl-*N,N,N',N'*-tetramethyluronim hexafluorophosphate

KOH = potassium hydroxide

$K_2CO_3$ = potassium carbonate

$POCl_3$ = phosphorous oxychloride

KOtBu= potassium t-butoxide

EDC or EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

DIPEA = diisopropylethylamine

HOBt = 1-hydroxybenzotriazole hydrate

m-CPBA = m-chloroperbenzoic acid

NaH = sodium hydride

NaOH = sodium hydroxide

$Na_2S_2O_3$ = sodium thiosulfate

Pd = palladium

Pd/C = palladium on carbon

min = minute(s)

L = liter

mL = milliliter

μL= microliter

g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT or rt = room temperature

$t_R$ = HPLC retention time (minutes)

sat or sat'd = saturated

In the Examples:

"HPLC (6 minute gradient)" refers to Keystone C18 Beta Basic column, 0.4 mL/min flow rate, 6 minute linear gradient elution (start solvent %B = 0; final solvent %B = 100), solvent A: acetonitrile + 0.025% TFA; solvent B = $H_2O$ + 0.025% TFA .

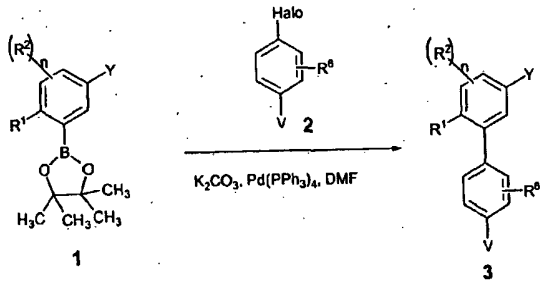
"HPLC (4 minute gradient)" refers to Keystone C18 Beta Basic column, 0.5 mL/min flow rate, 4 minute linear gradient elution (start solvent %B = 0; final solvent %B = 100), solvent A: acetonitrile + 0.025% TFA; solvent B = $H_2O$ + 0.025% TFA .

## Methods of Preparation

Compounds of formula I may be generally be prepared according to the following schemes and the knowledge of one skilled in the art. In addition to the documents incorporated by reference we disclose the following. Examples of methods useful for the production of compounds of this invention are illustrated in schemes 1-18.

Central to the construction of many of the compounds in this application is the formation of carbon-carbon bonds between aromatic systems using boronic esters or boronic acids and aryl halides. This chemistry is often referred to as "Suzuki" chemistry or as the Suzuki reaction.[1] Scheme 1 shows a synthetic route to key intermediates and final compounds in this invention.

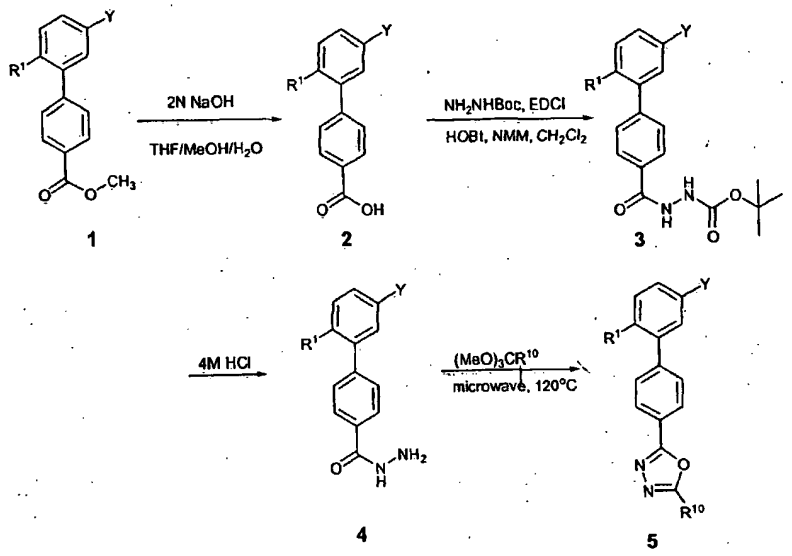
Scheme 1




The chemical functionality of the molecule may be changed after the key Suzuki coupling reaction. This is exemplified in Scheme 2. The oxadiazole

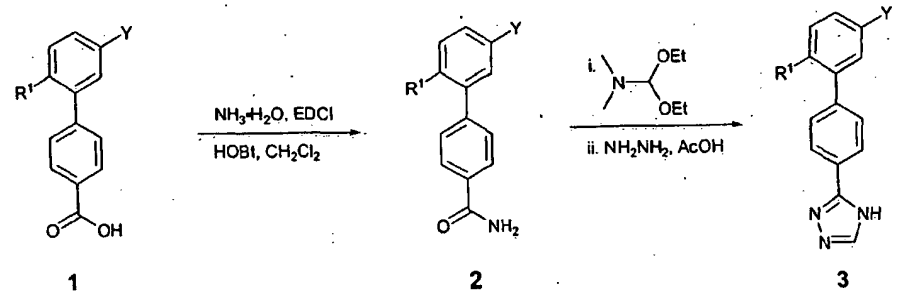
heterocycle is formed after the carbon-carbon bond formation of the Suzuki reaction. Additional methods are known to those skilled in the art to form heterocycles. For reference, methods disclosed by Dhar *et al* are cited.[2]

Scheme 2



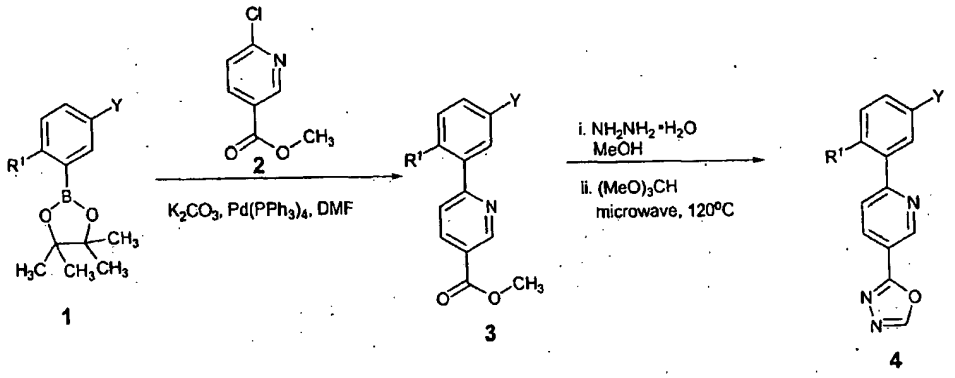

Scheme 3 depicts the formation of a triazole heterocycle on a biphenyl moiety.

Scheme 3



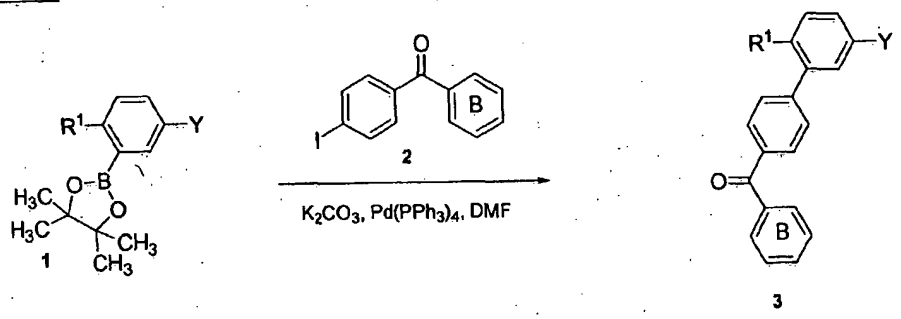

Scheme 4 depicts the formation of a key carbon bond between an aryl and heteroaryl systems followed by the formation of the terminal 5-membered ring heterocycle.

Scheme 4



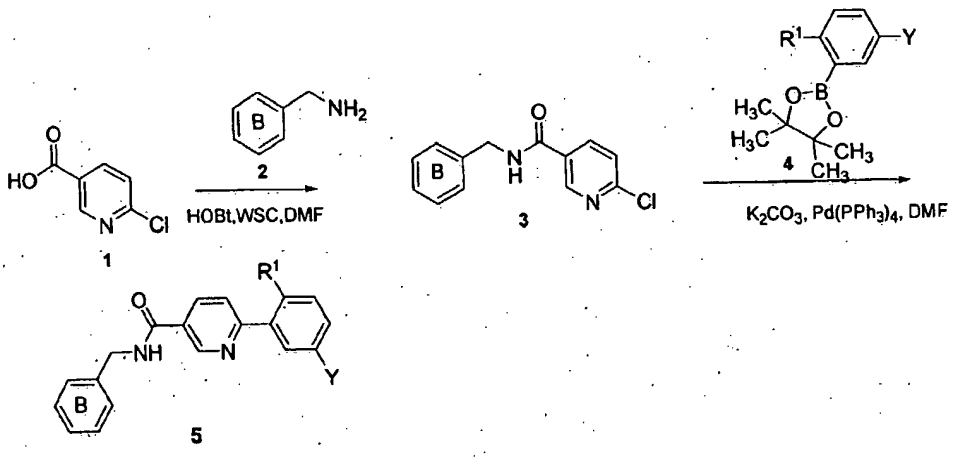

Scheme 5 depicts the formation of the biaryl ketone analogs. The terminal aryl residue (B) may be optionally substituted or may be replaced by an optionally substituted heteroaryl residue.

Scheme 5




Scheme 6 depicts the formation of aryl heteroaryl amides. The terminal aryl residue (B) may be optionally substituted or may be replaced by an optionally substituted heteroaryl residue.

Scheme 6

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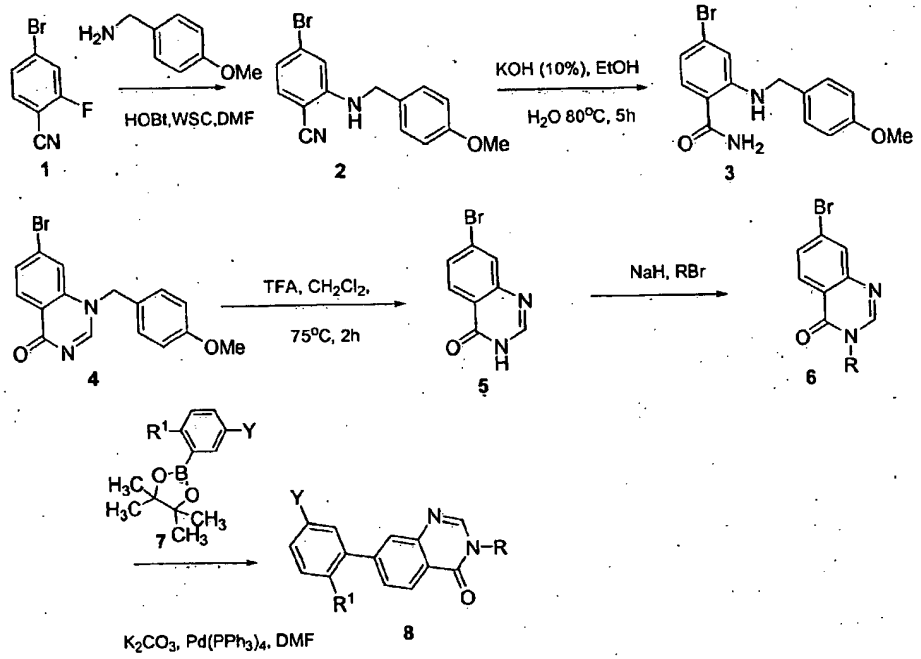
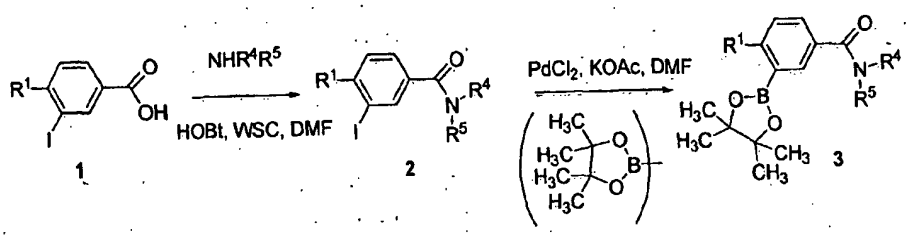
Scheme 7



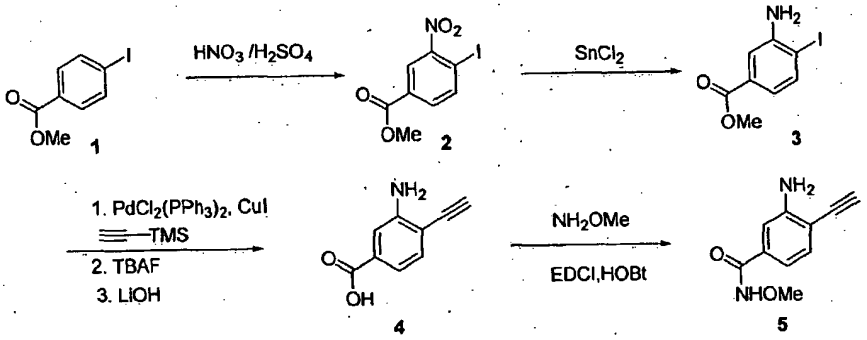

10 Scheme 8




Amines attached to aryl or heteroaryl ring systems are useful as intermediates in this invention. There are many methods of preparing such intermediates known to one skilled in the art of organic chemistry. Several methods of preparing amines useful to this invention are illustrated in schemes 9-11.

Substituted aniline of type (5) can be prepared from commercially available methyl 4-iodobenzoate as depicted in scheme 9. Nitration followed by reduction of the nitro group yields the aniline. Palladium-catalyzed coupling with ethynyltrimethylsilane, followed by desilylation and saponification gives the desired ethynyl-substituted aminobenzoic acid. Coupling with methoxyamine using coupling agent EDC affords the desired aniline (5).

Scheme 9

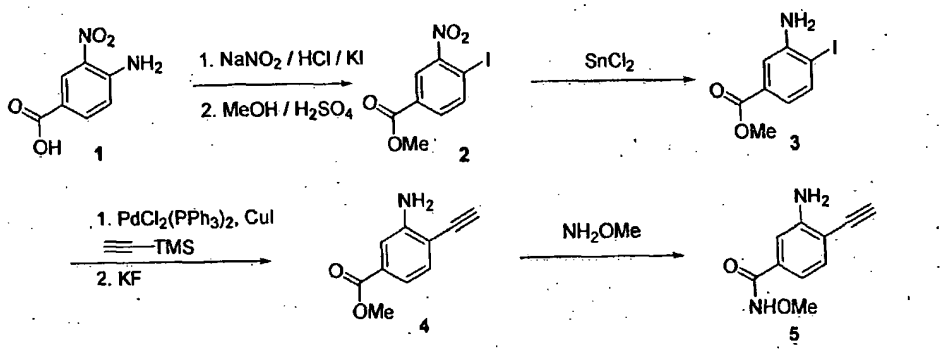



Eu. J. Org. Chem, 4607 (2001)

Alternatively, substituted aniline of type (5) can be prepared 4-amino-3-nitrobenzoic acid as depicted in scheme 10. Iodide substitution of the aryldiazonium salt, followed by esterification with methanol gives methyl 4-iodo-3-nitrobenzoate. The nitro group can be reduced by $SnCl_4$ to give the desired aniline. Palladium catalyzed coupling with ethynyltrimethylsilane, followed by

desilylation and saponification yields the ethynyl-substituted aminobenzoic acid. Coupling with methoxyamine using coupling agent EDC affords the desired aniline (5).

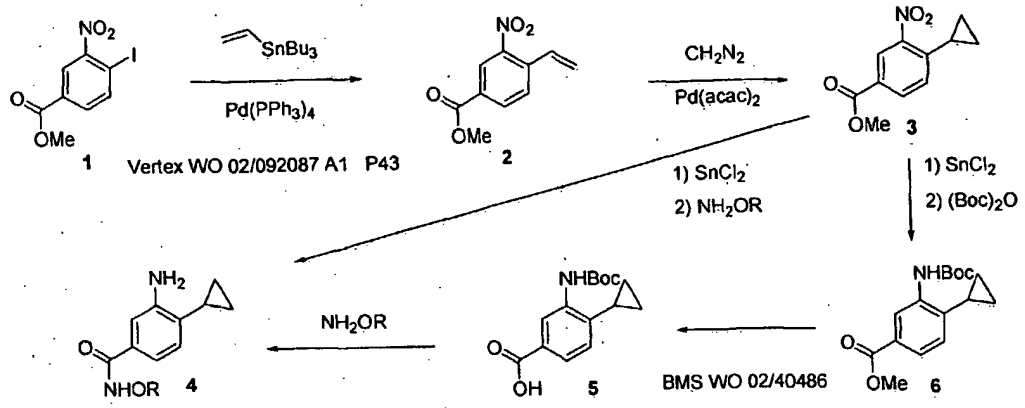
Scheme 10




Eu. J. Org. Chem, 4607 (2001)

As depicted in scheme 18, substituted aniline of type (4) can be prepared from intermediate methyl 4-iodo-3-nitrobenzoate, which can be synthesized as shown in scheme 10. Palladium catalyzed coupling with vinyltributyltin followed by carbene addition to the resulty styrene double bond gives the cyclopropyl substituted methyl nitrobenzoate. Reduction of the nitro group followed by Boc protection and saponification gives the protected 3-amino-4-cyclopropylbenzoic acid. Coupling with an alkoxyamine using coupling agent EDC affords the desired aniline (4).

Scheme 11



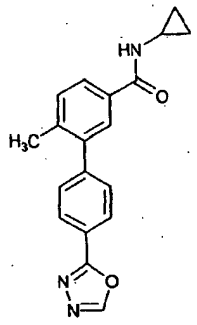

References of additional synthetic methods are as follows:

1) Organic Letters Vol. 4, No. 6, p 979-981 (2002) and references sited therein.
2) Bioorganic and Medicinal Chemistry Letters Vol. 12, 3125-3128 (2002) and references contained therein.

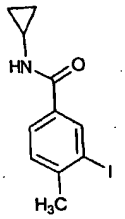
The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims. Abbreviations employed in the Examples are defined below. Compounds of the Examples are identified by the example and step in which they are prepared (for example, "1A" denotes the title compound of step A of Example 1), or by the example only where the compound is the title compound of the example (for example, "2" denotes the title compound of Example 2).

## Example 1

6-Methyl-4'-[1,3,4]oxadiazol-2-yl-biphenyl-3-carboxylic acid cyclopropylamide



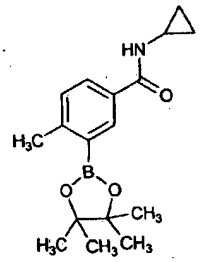
A. *N*-Cyclopropyl-3-iodo-4-methyl-benzamide



A solution of 3-iodo-4-methylbenzoic acid (10.5 g, 40 mmol), 1-(3-dimethlaminopropyl)-3-ethylcarbodiimide hydrochloride (9.2 g, 48 mmol) and cyclopropylamine (2.6 g, 45.6 mmol) in *N,N*-dimethylformamide (70 ml) was stirred at room temperature for 4 h. Water (250 mL) was added. The solution was extracted with ethyl acetate (200mL x 2), washed with saturated $K_2CO_3$ solution (200 mL) and water (200 mL). Organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure to give the desired product (11.8 g, 98%).

HPLC (6 minute gradient) $t_R$ = 3.39 min; MS m/z 302 (M + H)

B. *N*-Cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide

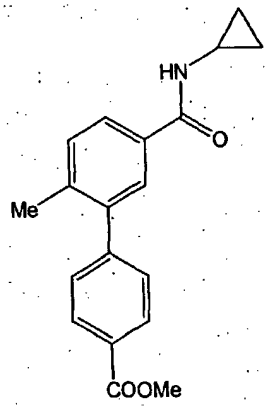


To a solution of the compound from part A (4.52 g, 15 mmol) and bis(pinacolato)diboron (4.05 g, 16 mmol) in 50 mL of dry *N,N*-dimethylformamide was added potassium acetate (4.4 g, 45 mmol) and followed by $PdCl_2$(pddf) (612 mg, 0.75 mmol). After the reaction mixture was stirred at 95°C for 5 hours, the reaction mixture was allowed to cool to room temperature. And then 100 mL of water was added. The resulting mixture was extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by

chromatography (hexanes : ethyl acetate = 2 : 1) to give the desired product as a colorless solid (3.1 g, 69%)

$^1$H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, $J$ = 1.9 Hz, 1H), 7.81 (dd, $J$ = 2.1, 7.9 Hz, 1H), 7.23 (d, $J$ = 8.0 Hz, 1H), 6.29 (brs., 1H), 2.90 (m, 1H), 2.56 (s, 3H), 1.36 (s, 12H), 0.85 (m, 2H), 0.64 (m, 2H) ppm.
HPLC (4 minute gradient) $t_R$ = 2.62 min; MS m/z 302 (M+H).

C. 5'-Cyclopropylcarbamoyl-2'-methyl-biphenyl-4-carboxylic acid methyl ester

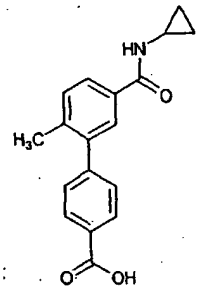



To a solution of 4-iodo-benzoic acid methyl ester (262 mg, 1.0 mmol) and the compound from part B (301 mg, 1.0 mmol) in 3 mL of dry *N*,*N*-dimethylformamide was added potassium carbonate (276 mg, 2.0 mmol) and followed by $Pd(PPh_3)_4$ (58 mg, 0.05 mmol). After the reaction mixture was stirred at 100°C for 2 hours, the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure. The residue was diluted with 80 mL of ethyl acetate and washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by chromatography (hexanes : ethyl acetate = 2 : 1) to give a colorless solid (280 mg, 91%)

$^1$H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, $J$ = 8.1 Hz, 2H), 7.68 (dd, $J$ = 1.9, 7.9 Hz, 1H), 7.60 (d, $J$ = 1.8 Hz, 1H), 7.37 (d, $J$ = 8.1 Hz, 2H), 7.31 (d, $J$ = 8.0 Hz, 1H), 6.53 (brs., 1H), 3.94 (s, 3H), 2.89 (m, 1H), 2.27 (s, 3H), 0.85 (m, 2H), 0.62 (m, 2H) ppm.

HPLC (4 minute gradient) $t_R$ = 2.39 min; MS m/z 310 (M+H).

D. 5'-Cyclopropylcarbamoyl-2'-methyl-biphenyl-4-carboxylic acid

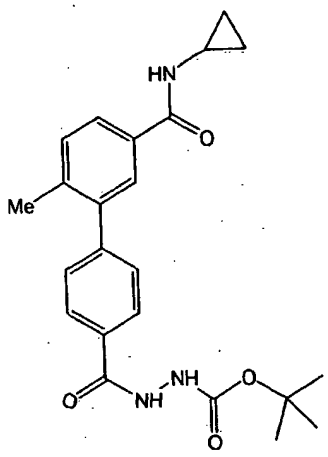



To a solution of the compound from part C (270 mg, 0.87 mmol) in 3 mL of tetrahydrofuran, 1 mL of methanol and 1 mL of water was added sodium hydroxide (2M, 1.3 mL, 2.62 mmol) at 20°C. The reaction mixture was stirred at that temperature overnight and then the clear solution was neutralized by dropwise addition of 2N aqueous hydrochloric acid. The resulting mixture was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated to give the desired compounds as a colorless solid (220 mg, 86%), which was used to the next step without further purification.

$^1$H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, $J$ = 8.5 Hz, 2H), 7.69 (dd, $J$ = 2.0, 8.0 Hz, 1H), 7.61 (d, $J$ = 1.9 Hz, 1H), 7.44 (d, $J$ = 8.5 Hz, 2H), 7.36 (d, $J$ = 7.9 Hz, 1H), 6.26 (brs., 1H), 2.91 (m, 1H), 2.31 (s, 3H), 0.92 (m, 2H), 0.62 (m, 2H) ppm.

HPLC (4 minute gradient) $t_R$ = 1.91 min; MS m/z 296 (M+H).

E. *N'*-(5'-Cyclopropylcarbamoyl-2'-methyl-biphenyl-4-carbonyl)-hydrazinecarboxylic acid tert-butyl ester

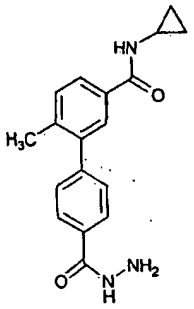



To a solution of the compound from part D (59 mg, 0.20 mmol) and the hydrazine (33 mg, 0.25 mmol) in 2 mL of dry methylene chloride was added 1-hydroxybenzotriazole (46 mg, 0.30 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (57 mg, 0.30 mmol) and 4-methylmorpholine (61 mg, 0.6 mmol) at 20°C. The reaction mixture was stirred at 20°C for 3 hours. The solvent was removed under reduced pressure. The residue was diluted with 60 mL of ethyl acetate and washed with water (10 mL), 2N aqueous HCl (10 mL), *sat.* aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated to give the desired compounds as a colorless solid (75 mg, 91%), which was pure enough to be used to the next step without further purification.

$^1H$ NMR (300 MHz, $CDCl_3$): δ 8.28 (brs., 1H), 7.86 (d, $J$ = 8.3 Hz, 2H), 7.66 (dd, $J$ = 1.9, 7.9 Hz, 1H), 7.55 (d, $J$ = 1.9 Hz, 1H), 7.35 (d, $J$ = 8.3 Hz, 2H), 7.31 (d, $J$ = 8.1 Hz, 1H), 6.79 (brs., 1H), 6.38 (brs., 1H), 2.90 (m, 1H), 2.25 (s, 3H), 1.51 (s, 9H), 0.85 (m, 2H), 0.62 (m, 2H) ppm.

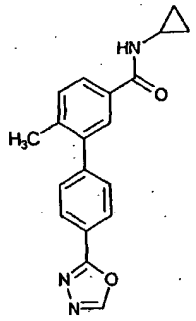
HPLC (4 minute gradient) $t_R$ = 2.10 min; MS m/z 410 (M+H)

F. 4'-Hydrazinocarbonyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide



To a solution of the compound from part E (70 mg, 0.17 mmol) in 2 mL of methanol was added HCl (4N, 0.42 mL, 0.17 mmol) in 1,4-dioxane. The reaction mixture was stirred at room temperature for 2 hours and then concentrated under reduced pressure to give a colorless solid (52 mg, 88%).

G. 6-Methyl-4'-[1,3,4]oxadiazol-2-yl-biphenyl-3-carboxylic acid cyclopropylamide

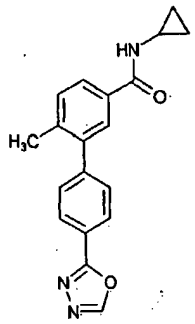


The mixture of the compound from part F (15 mg, 0.044 mmol) in 0.5 mL of trimethyl orthoformate was stirred at 120°C in microwave for 10 minutes. The solvent was removed under reduced pressure. The residue was diluted with 30 mL of ethyl acetate and washed with *sat.* aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by preparative TLC sheet (hexanes : ethyl acetate = 1 : 1) to give the desired product as a colorless solid (12 mg, 87%).

$^1$H NMR (300 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.15 (d, $J$ = 8.6 Hz, 2H), 7.67 (dd, $J$ = 2.0, 7.9 Hz, 1H), 7.63 (d, $J$ = 1.9 Hz, 1H), 7.48 (d, $J$ = 8.6 Hz, 2H), 7.35 (d, $J$ = 7.9 Hz, 1H), 6.30 (brs., 1H), 2.90 (m, 1H), 2.31 (s, 3H), 0.86 (m, 2H), 0.63 (m, 2H) ppm. HPLC (4 minute gradient) $t_R$ = 1.92 min; MS m/z 320 (M+H).

H. 6-Methyl-4'-[1,3,4]oxadiazol-2-yl-biphenyl-3-carboxylic acid cyclopropylamide

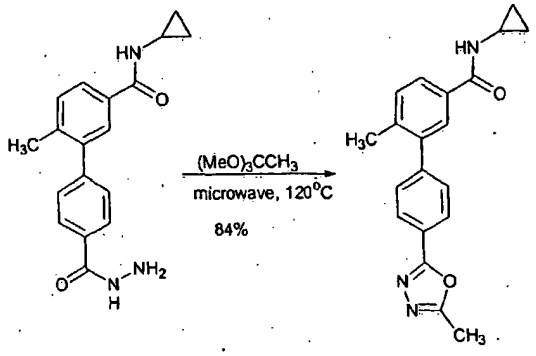
*(An alternative synthesis of compound 1)*




To a solution of the compound from part C (130 mg, 0.42 mmol) in 2 mL of methanol was added 2 mL of hydrazine monohydrate. The reaction mixture was stirred at room temperature for 1 hour. The solvents were removed to give a foam (120 mg). To a solution of this foam (100 mg, 0.32 mmol) in 3 mL of trimethyl orthoformate was added one drop of concentrated HCl. The reaction mixture was stirred at 120°C in microwave for 10 minutes. The solvent was removed under reduced pressure. The residue was diluted with 80 mL of ethyl acetate and washed with *sat.* aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by chromatography (hexanes : ethyl acetate = 1 : 1) to give the desired product as a colorless solid (89 mg, 79% for two steps)

## Example 2

6-Methyl-4'-(5-methyl-[1,3,4]oxadiazol-2-yl)-biphenyl-3-carboxylic acid cyclopropylamide

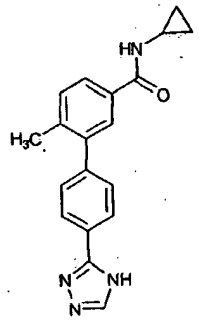



The mixture of the compound from part 1F (21 mg, 0.061 mmol) in 1.5 mL of trimethyl orthoacetate was stirred at 120°C in microwave for 10 minutes. The solvent was removed under reduced pressure. The residue was diluted with 30 mL of ethyl acetate and washed with *sat.* aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by preparative TLC sheet (hexanes : ethyl acetate = 1 : 1) to give the desired product as a colorless solid (12 mg, 87%).

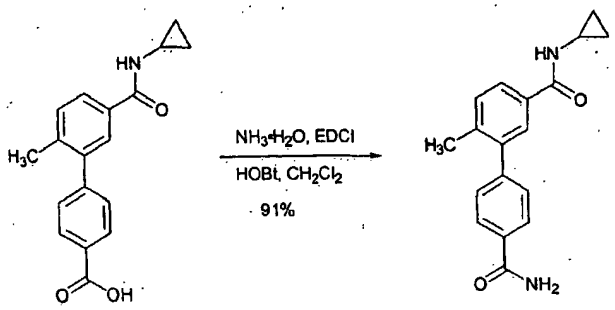
HPLC (4 minute gradient) $t_R$ = 2.10 min; MS m/z 334 (M+H).

## Example 3

6-Methyl-4'-(4H-[1,2,4]triazol-3-yl)-biphenyl-3-carboxylic acid cyclopropylamide



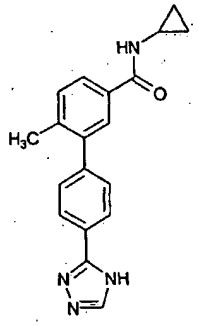

A. 6-Methyl-biphenyl-3,4'-dicarboxylic acid 4'-amide 3-cyclopropylamide




To a solution of the compound from 1D (50 mg, 0.17 mmol) and the ammonium hydroxide (30%, 0.3 mL) in 2 mL of methylene chloride was added 1-hydroxybenzotriazole (39 mg, 0.25 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (49 mg, 0.25 mmol) at 20°C. The reaction mixture was stirred at 20°C for 4 hours. The solvent was removed under reduced pressure. The residue was diluted with 60 mL of ethyl acetate and washed with water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by preparative TLC sheet (hexanes : ethyl acetate = 1 : 1) to give the desired product as a colorless solid (12 mg, 91%)

HPLC (4 minute gradient) $t_R$ = 1.68 min; MS m/z 295 (M+H).

B. 6-Methyl-4'-(4H-[1,2,4]triazol-3-yl)-biphenyl-3-carboxylic acid cyclopropylamide



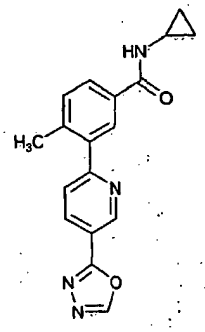

A mixture of the compound from part A (20 mg, 0.068 mmol) in 1.2 mL of *N,N*-dimethylformamide diethyl acetal was stirred at 80°C for 3 hours. The solvent was removed under reduced pressure. The residue was dissolved in 1 mL of acetic acid and anhydrous hydrazine (4.4 mg, 0.136 mmol) was added to the mixture. The reaction mixture was stirred at 90°C for 2 hours. The solvent was removed under

reduced pressure. The crude product was purified by preparative TLC sheet (methylene chloride : mathanol = 10 : 1) to give the desired product as a colorless solid (15 mg, 69%).

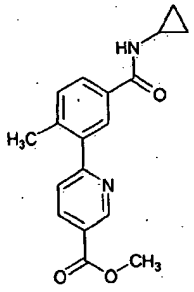
HPLC (4 minute gradient) $t_R$ = 1.73 min; MS m/z 319 (M+H).

## Example 4

*N*-Cyclopropyl-4-methyl-3-(5-[1,3,4]oxadiazol-2-yl-pyridin-2-yl)-benzamide



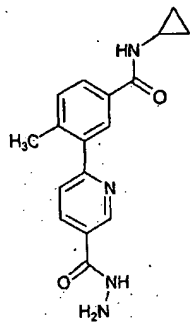
A. 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-nicotinic acid methyl ester



To a solution the 6-chloro-nicotinic acid methyl ester (410 mg, 2.40 mmol) and the compound from 1B (602 mg, 2.0 mmol) in 10 mL of dry *N*,*N*-dimethylformamide was added potassium carbonate (663 mg, 4.8 mmol) and followed by $Pd(PPh_3)_4$ (115 mg, 0.10 mmol). After the reaction mixture was stirred at 95°C for 2 hours, the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure. The residue was diluted with 100 mL of ethyl acetate and washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by chromatography (hexanes :

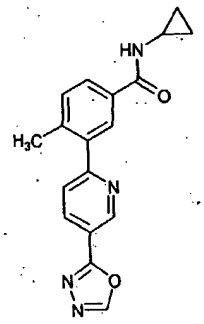
ethyl acetate = 1 : 1) to give the desired product as a colorless solid (320 mg, 52%). HPLC (4 minute gradient) $t_R$ = 1.91 min; MS m/z 311 (M+H).

B. N-Cyclopropyl-3-(5-hydrazinocarbonyl-pyridin-2-yl)-4-methyl-benzamide



To a solution of the compound from part A (80 mg, 0.26 mmol) in 2 mL of methanol was added 2 mL of hydrazine monohydrate. The reaction mixture was stirred at room temperature for 2 hour. The solvents were removed to give the desired compound as a foam (72 mg).

C. *N*-Cyclopropyl-4-methyl-3-(5-[1,3,4]oxadiazol-2-yl-pyridin-2-yl)-benzamide



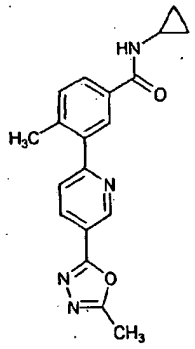
To a solution of the compound from part B, 2 mL of trimethyl orthoformate was added one drop of concentrated HCl. The reaction mixture was stirred at 120°C in microwave for 10 minutes. The solvent was removed under reduced pressure. The residue was diluted with 30 mL of ethyl acetate and washed with *sat.* aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by preparative TLC sheet

(methylene chloride : methanol = 10 : 1) to give the desired product as a colorless solid (12 mg, 52% for two steps).

HPLC (4 minute gradient) $t_R$ = 1.65 min; MS m/z 321 (M+H).

## Example 5

*N*-Cyclopropyl-4-methyl-3-[5-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-benzamide

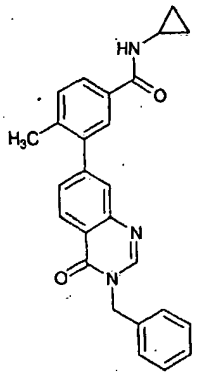



To the compound from 4B (20 mg, 0.065 mmol) in 2 mL of trimethyl orthoacetate was added one drop of concentrated HCl. The reaction mixture was stirred at 120°C in microwave for 10 minutes. The solvent was removed under reduced pressure. The residue was diluted with 30 mL of ethyl acetate and washed with *sat.* aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by preparative TLC sheet (methylene chloride : methanol = 10 : 1) to give the titled compound as a colorless solid (14 mg, 65%)

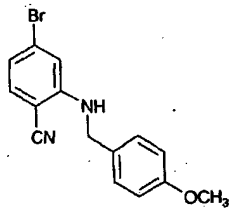
HPLC (4 minute gradient) $t_R$ = 1.69 min; MS m/z 335 (M+H).

## Example 6

3-(3-Benzyl-4-oxo-3,4-dihydro-quinazolin-7-yl)-N-cyclopropyl-4-methyl-benzamide

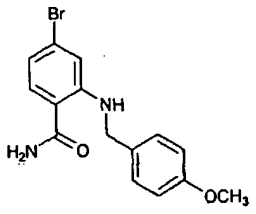


A. 4-Bromo-2-(4-methoxy-benzylamino)-benzonitrile



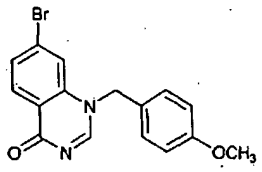
A solution of 5-bromo-2-fluorobenzonitrile (3 g), 4-methoxybenzylamine (2.2 g), and triethyl amine (3 ml) in DMSO (5 ml) was heated at 120 °C for 5 h. The solution was partitioned between water and ethyl acetate. The combined organic extract was washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was chromatographed to give the desired product (2.6 g, 81%) HPLC (6 minute gradient) $t_R$ = 4.33 min; MS m/z 315.09, 317.08 $(M + H]^+$

B. 4-Bromo-2-(4-methoxy-benzylamino)-benzamide



The compound from part A was heated in a KOH solution (10%) of EtOH/$H_2O$, 50%, 100 ml) at 80 °C for 5 h. The resulting precipitate was filtrated and dried to yield 4-bromo-2-(4-methoxy)benzylbenzamide (2.0g, 95%).

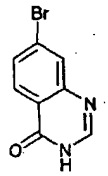
C. 7-Bromo-1-(4-methoxy-benzyl)-1H-quinazolin-4-one




The compound from part B (1.8 g) was heated in a solution of N,N-dimethylformamide dimethyl acetal (3 ml) and DMF (2 ml) at 130 °C for 4 h. Then the solvent was removed and water (2 ml) was added. The precipitate was filtrated and washed with water and 50% ethyl acetate /hexane. 1.55 g of the desired compound is obtained (yield: 75%).

$^1$H NMR (300 MHz, CDCl3) δ 3.84 (s, 3H), 5.24 (s, 2H), 6.97 (d, 2 H, J = 6.7 Hz), 7.20 (d, 2H, J = 6.7 Hz), 7.48 (s, 1H), 7.60 (d, 1H, J = 8.5 Hz), 8.22 (d, 1 H, J = 8.5 Hz), 8.34 (s, 1H)

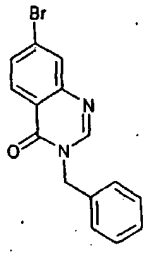
D. 7-Bromo-3H-quinazolin-4-one




The compound from part C was treated with TFA/dichloroethane (50%, 3 ml) at 75 °C for 2h. The solvent was removed with nitrogen and ethyl acetate was added. The resulting precipitate was filtrated to yield the desired compound (1.0g, 96%).

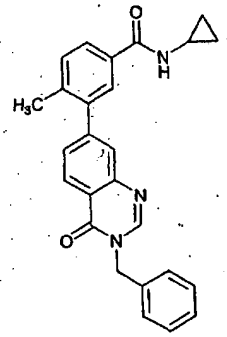
HPLC (4 minute gradient) $t_R$ = 1.61 min; MS m/z 225.25, 227.21 $(M + H)^+$

E. 3-Benzyl-7-bromo-3H-quinazolin-4-one



To a solution of the compound from part D (225 mg, 1 mmol) in dry DMF (4 ml) was added sodium hydride (30 mg). The solution was cooled down to 0 °C and benzyl bromide (171 mg) was added. Then the mixture was allowed to react at room temperature for 10 min. after adding water (15 ml), the precipitate was filtrated and washed with water and dried in air. 170 mg of desired product was obtained (yield: 54%).HPLC (4 minute gradient) $t_R$ = 2.54 min; MS m/z 315.27, 317.0 $(M + H]^+$

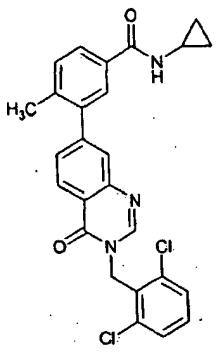
F. 3-(3-Benzyl-4-oxo-3,4-dihydro-quinazolin-7-yl)-N-cyclopropyl-4-methyl-benzamide



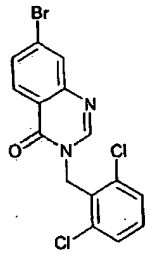
To a solution of the compound from part E (157.5 mg, 0.5 mmol), the compound from 1B (150 mg, 0.5 mmol) and $K_2CO_3$ (100 mg) in DMF (5 ml) under nitrogen was added $Pd(PPh_3)_4$ (40 mg). The mixture was heated at 95 °C for 3 h. Water (8 ml) was added and the solution was extracted with ethyl acetate (5 ml x 2) and dried over $Na_2SO_4$. Evaporation of the solvent give a residue which is separated by column chromatography (Hexane: EtOAc = 1:1). 146 mg of the desired product was obtained (yield: 71%). HPLC (4 minute gradient) $t_R$ = 2.15 min; MS m/z 410.47 $(M + H]^+$

## Example 7

N-Cyclopropyl-3-[3-(2,6-dichloro-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide

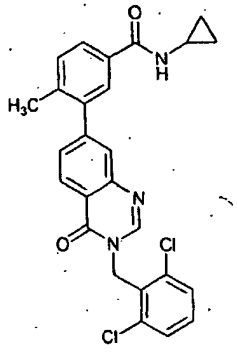


A. 7-Bromo-3-(2,6-dichloro-benzyl)-3H-quinazolin-4-one



To a solution of the compound from 6D (113 mg, 0.5 mmol) in dry DMF (2 ml) was added sodium hydride (20 mg). The solution was cooled down to 0 °C and 2,6-dichlorobenzy chloride (100 mg, 0.0) was added. Then the mixture was allowed to react at room temperature for 10 min. after adding water (4 ml), the precipitate was filtrated and washed with water and dried in air. 117 mg of desired product was obtained (yield: 61%). HPLC (4 minute gradient) $t_R$ = 3.11 min; MS m/z 383.40, 385.13, 386.93 $(M + H)^+$

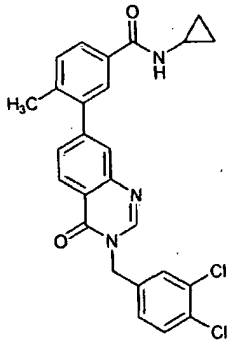
B. N-Cyclopropyl-3-[3-(2,6-dichloro-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide



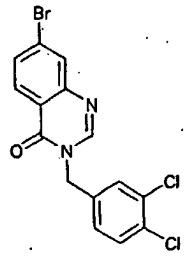
To a solution of the compound from part A (38.5 mg, 0.1 mmol), the compound from 1B (30 mg, 0.1 mmol) and $K_2CO_3$ (30 mg) in DMF (2 ml) under nitrogen was added $Pd(PPh_3)_4$ (10 mg). The mixture was heated at 95 °C for 3 h. Water (3 ml) was added and the solution was extracted with ethyl acetate (4 ml x 2) and dried over $Na_2SO_4$. Evaporation of the solvent give a residue which is separated by preparative TLC plate (DCM: EtOAc = 1:1). 46 mg of the desired product was obtained (yield: 95%). HPLC ( 4 minutes gradient) $t_R$ = 2.59 min; MS m/z 478.80, 480.33

## Example 8

N-Cyclopropyl-3-[3-(3,4-dichloro-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide

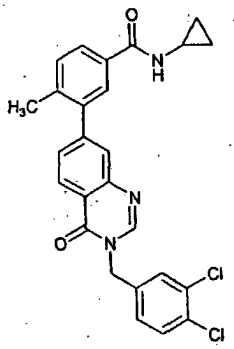


A. 7-Bromo-3-(3,4-dichloro-benzyl)-3H-quinazolin-4-one



To a solution of the compoundf from 6D (113 mg, 0.5 mmol) in dry DMF (2 ml) was added sodium hydride (20 mg). The solution was cooled down to 0 °C and 3,4-dichlorobenzy bromide (120 mg, 0.5 mmol)) was added. Then the mixture was allowed to react at room temperature for 10 min. after adding water (4 ml), the precipitate was filtrated and washed with water and dried in air. 110 mg of desired product was obtained (yield: 57%). HPLC (4 minute gradient) $t_R$ = 3.24 min; MS m/z 383.33, 385.07, 386.87 $(M + H)^+$

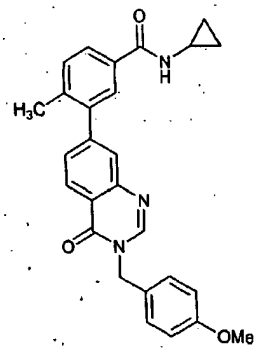
B. N-Cyclopropyl-3-[3-(3,4-dichloro-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide



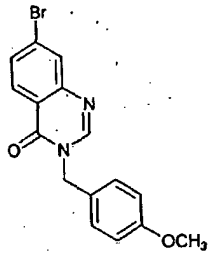
To a solution of the compound from part A (38.5 mg, 0.1 mmol), compound 1B (30 mg, 0.1 mmol) and $K_2CO_3$ (30 mg) in DMF (2 ml) under nitrogen was added $Pd(PPh_3)_4$ (10 mg). The mixture was heated at 95 °C for 3 h. Water (3 ml) was added and the solution was extracted with ethyl acetate (4 ml x 2) and dried over $Na_2SO_4$. Evaporation of the solvent give a residue which is separated by preparative TLC plate (DCM: EtOAc = 1:1). 46 mg of the desired product was obtained (yield: 90%). HPLC (4 minute gradient) $t_R$ = 2.78 min; MS m/z 478.80, 480.33 $(M + H)^+$

## Example 9

N-Cyclopropyl-3-[3-(4-methoxy-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide

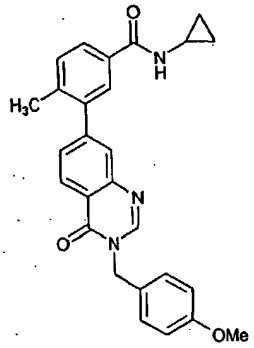


A. 7-Bromo-3-(4-methoxy-benzyl)-3H-quinazolin-4-one



To a solution of the compound 6D (113 mg, 0.5 mmol) in dry DMF (2 ml) was added sodium hydride (20 mg). The solution was cooled down to 0 °C and 4-methoxycarbonylbenzy bromide (114 mg) was added. Then the mixture was allowed to react at room temperature for 10 min. after adding water (4 ml), the precipitate was filtrated and washed with water and dried in air. 130 mg of desired product was obtained (yield: 67.5%). HPLC (4 minute gradient) $t_R$ = 2.42 min; MS m/z 373.33, 375.07 $(M + H]^+$

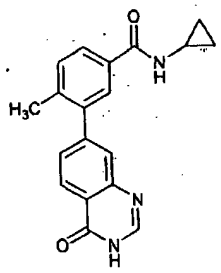
B. N-Cyclopropyl-3-[3-(4-methoxy-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide




To a solution of the compound from part A ( 37 mg, 0.1 mmol), compound 1B (30 mg, 0.1 mmol) and $K_2CO_3$ (30 mg) in DMF (2 ml) under nitrogen was added $Pd(PPh_3)_4$ (10 mg). The mixture was heated at 95 °C for 3 h. Water (3 ml) was added and the solution was extracted with ethyl acetate (4 ml x 2) and dried over $Na_2SO_4$. Evaporation of the solvent give a residue which was separated by preparative TLC plate (DCM: EtOAc = 1:1). 46 mg of desired product was obtained (yield: 68%). HPLC (4 minute gradient) $t_R$ = 2.12min; MS m/z 468.33 $(M + H]^+$

## Example 10

N-Cyclopropyl-4-methyl-3-(4-oxo-3,4-dihydro-quinazolin-7-yl)-benzamide

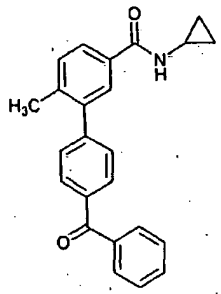



To a solution of the compound 6D ( 23 mg, 0.1 mmol), compound 1B (30 mg, 0.1 mmol) and $K_2CO_3$ (30 mg) in DMF (2 ml) under nitrogen was added $Pd(PPh_3)_4$ (10 mg). The mixture was heated at 95 °C for 3 h. Water (3 ml) was added and the solution was extracted with ethyl acetate (4 ml x 2) and dried over $Na_2SO_4$. Evaporation of the solvent give a residue which was separated by preparative TLC

plate ( DCM: EtOAc = 1:1). 23 mg of title compound was obtained (yield: 72%). HPLC (4 minute gradient) $t_R$ = 1.61 min; MS m/z 320.15 $(M + H]^+$

## Example 11

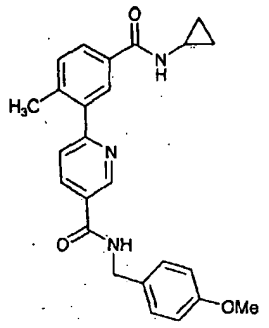
4'-Benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide



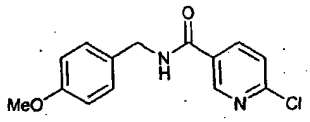
To a solution of 4-iodobenzophenone (62 mg, 0.2 mmol), 1B (60 mg, 0.2 mmol) and $K_2CO_3$ (50 mg) in DMF (2 ml) under nitrogen was added $Pd(PPh_3)_4$ (20 mg). The mixture was heated at 100 °C for 2 h. Water (4 ml) was added and the solution was extracted with ethyl acetate (5 ml x 2) and dried over $Na_2SO_4$. Evaporation of the solvent give a residue which is separated by preparative TLC plate (Hexane: EtOAc = 1:1). 53 mg of the desired product was obtained (yield: 75%). HPLC (6 minute gradient) $t_R$ = 4.15 min; MS m/z 355.95 $(M + H]^+$

## Example 12

6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-(4-methoxy-benzyl)-nicotinamide

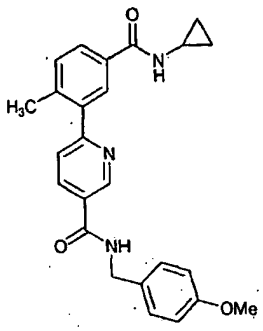


A. 6-Chloro-N-(4-methoxy-benzyl)-nicotinamide



A solution of 6-chloronicotinic acid (473 mg, 3 mmol), 4-methoxybenzylamine (412 mg, 3 mmol), 1-(3-dimethlaminopropyl)-3-ethylcarbodiimide hydrochloride (700 mg, 3.6 mmol) and HOBt (200 mg)) in DMF (15 ml) was stirred at room temperature for 3 h. Water (100 ml) was added. The solution was extracted with ethyl acetate (150ml X 2), washed with saturated $K_2CO_3$ solution (100 ml) and water (200 ml). Organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure to give the desired product (810mg, 97%). HPLC (6 minute gradient) $t_R$ = 3.12 min; MS m/z 275.00, 276.95 $(M + H)^+$

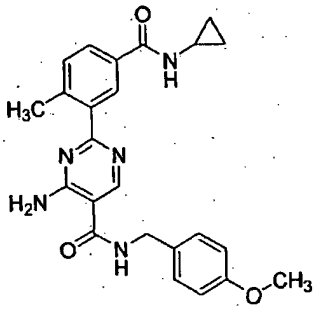
B. 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-(4-methoxy-benzyl)-nicotinamide



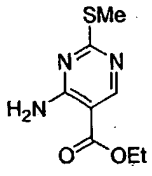
To a solution of the compound from part A (28 mg, 0.1 mmol), compound 1B (30 mg, 0.1 mmol) and $K_2CO_3$ (30 mg) in DMF (2 ml) under nitrogen was added $Pd(PPh_3)_4$ (10 mg). The mixture was heated at 95 °C for 3 h. Water (3 ml) was added and the solution was extracted with ethyl acetate (4 ml x 2) and dried over $Na_2SO_4$. Evaporation of the solvent gave a residue which is separated by preparative TLC plate (EtOAc). 32 mg of the desired product product was obtained (yield: 76%). HPLC (6 minute gradient) $t_R$ = 3.01 min; MS m/z 416.16 $(M + H)^+$

## Example 13

*N*-(4-Methoxybenzyl)-2-[(5-cyclopropylaminocarbonyl)-2-methylphenyl]-4-aminopyrimidine-5-carboxyamide

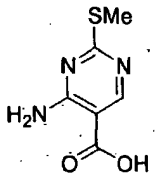


A. Ethyl 4-amino-2-methylmercaptopyrimidine-5-carboxylate



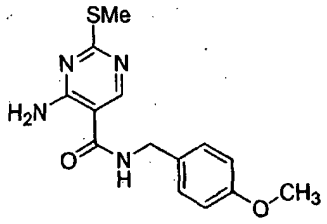
Iodomethane (2.6 g, 18 mmol) was added to the hot solution (~50 °C) of ethyl 4-amino-2-mercaptopyrimidine-5-carboxylate (3.0 g, 15 mmol) in *N,N*-dimethylformamide (150 mL) and stirred at room temperature for 20 min. Solvent was removed *in vacuo* and the solid residue was washed by water. After dried *in vacuo*, desired product was obtained as a white solid (3.1 g, 97%).
HPLC (4 minute gradient) $t_R = 2.14$ min; MS m/z 214.1 $(M + H)^+$

B. 4-Amino-2-methylmercaptopyrimidine-5-carboxylic acid




4-Amino-2-methylmercaptopyrimidine-5-carboxylate (1.5 g, 7 mmol) was suspended in the solution of lithium hydroxide (340 mg, 14 mmol) in methanol (10 mL) and water (5 mL) and stirred at 60 °C over night. Solid was filtered out and filtrate was collected. Solvent was removed under reduce pressure. Residue was dissolved in water and was neutralized by acetic acid till pH ~ 5. White solid thus formed was filtered out and dried *in vacuo* (0.72 g, 55%).
HPLC (4 minute gradient) $t_R = 0.55$ min; MS m/z 186.08 $(M + H)^+$

C. *N*-(4-Methoxybenzyl) 4-amino-2-methylmercaptopyrimidine-5-carboxyamide

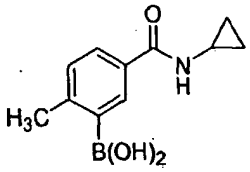



To a solution of 4-amino-2-methylmercaptopyrimidine-5-carboxylic acid (185 mg, 1 mmol) and *p*-methoxybenzyl amine (164 mg, 1.2 mmol) in *N,N*-dimethylformamide was added 1-hydroxybenzotriazole (92 mg, 92 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarboiimide hydrochloride (229 mg, 1.2 mmol).

The reaction mixture was stirred at room temperature over night. The solvent was removed under reduce pressure. The residue was dissolved in ethyl acetate (30 mL) and washed by water (30 mL) and brine (30 mL), dried over sodium sulfate, and the solvent was ecaporated. The residue was purified by column chromatography (hexanes : ethyl acetate = 1 :1) to give the desired product as a white powder (245 mg, 81%).

HPLC (4 minute gradient) $t_R$ = 2.09 min; MS m/z 305.08 $(M+H)^+$

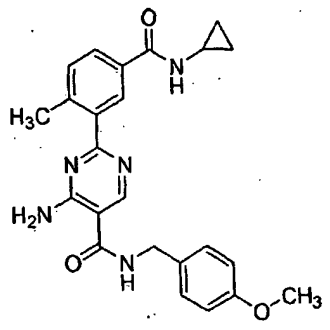
D. 5-Cyclopropylaminocarbonyl-2-methylboronic acid




Sodium periodate (4.8 g, 22.5 mmol) was added to the solution of *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide (2.25 g, 7.5 mmol) in tetrahydrofuran (80 mL) and water (20 mL). The mixture was stirred until homogeneous. Then 2N hydrochloro acid (3.0 mL) was added and stirred at room temperature over night. Tetrahydrofuran was removed *in vacuo* and the residue was suspended in ethyl acetate (100 mL), washed by water (100 mL), brine (100 mL), dried over sodium sulfate. Solvent was evaporated to give the desired product as a white solid (1.4 g, 85%).

HPLC (4 minute gradient) $t_R$ = 1.30 min; MS m/z 219.9 $(M+H)^+$

E. *N*-(4-Methoxybenzyl)-2-[(5-cyclopropylaminocarbonyl)-2-methylphenyl]-4-aminopyrimidine-5-carboxyamide

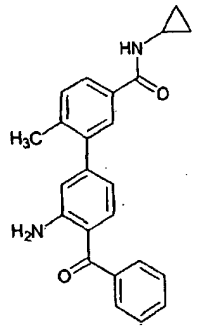


5-Cyclopropylaminocarbonyl-2-methylboronic acid (209 mg, 0.96 mmoL), tris(dibenzylideneacetone)dipalladium (0) (37 mg, 0.004 mmol), tris(2-furyl)phosphine (74 mg, 0.4 mmol) and copper (I) thiophene-2-carboxylate (198 mg, 1.6 mmol) were put in the flask and flushed with nitrogen. *N*-(4-Methoxybenzyl) 4-amino-2-methylmercaptopyrimidine-5-carboxyamide (245 mg, 0.8 mmol) in tetrahydrofuran (10 mL) was added to the flask and stirred at 50 °C in the nitrogen atmosphere over night. Solvent was removed *in vacuo*. The residue was suspended in ethyl acetate (50 mL) and washed by conc. aminohydroxide (20 mL), brine (50 mL) and dried over sodium sulfate. The residue was purified by column chromatography (hexanes : ethyl acetate = 1 :1) to give the desired product as a light yellow solid (49 mg, 14%).

HPLC (4 minute gradient) $t_R$ = 2.04 min; MS m/z 432.36 $(M + H)^+$

## Example 14

3'-Amino-4'-benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide



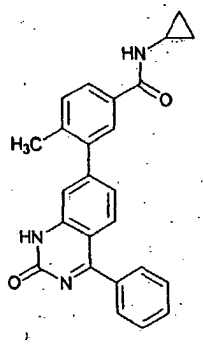
To a solution the (2-Amino-4-bromo-phenyl)-phenyl-methanone (276 mg, 1.0

mmol) and *N*-Cyclopropyl-3-iodo-4-methyl-benzamide (301 mg, 1.0 mmol) in 5 mL of methyl sulfoxide was added potassium carbonate (276 mg, 2.0 mmol) and followed by $Pd(PPh_3)_4$ (58 mg, 0.05 mmol). After the reaction mixture was stirred at 95°C for 4 hours, the reaction mixture was allowed to cool to room temperature and 10 mL of water was added to the mixture. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by chromatography (hexanes : ethyl acetate = 1 : 1) to give the desired compound as a colorless solid (180 mg, 49%).

HPLC (6 minute gradient) $t_R$ = 3.89 min; MS m/z 371 (M+H).

## Example 15

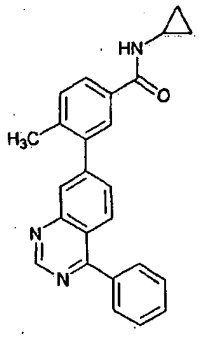
*N*-Cyclopropyl-4-methyl-3-(2-oxo-4-phenyl-1,2-dihydro-quinazolin-7-yl)-benzamide




The mixture of 3'-Amino-4'-benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide from Example 14 (19 mg, 0.051 mmol) and urea (3.7 mg, 0.062 mmol) in 0.5 mL acetic acid was stirred at 120°C for 4 hours. The solvents were removed under reduced pressure. The crude product was purified by preparative TLC sheet (methylene chloride : methanol = 10 : 1) to give a colorless solid (12 mg, 59%). HPLC (6 minute gradient) $t_R$ = 2.88 min; MS m/z 396 (M+H).

## Example 16

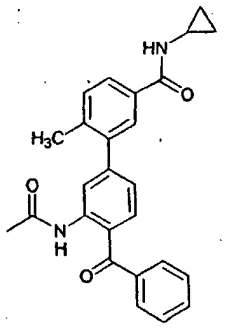
*N*-Cyclopropyl-4-methyl-3-(4-phenyl-quinazolin-7-yl)-benzamide



The mixture of 3'-Amino-4'-benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide from Example 15 (20 mg, 0.054 mmol) and formamide (2.9 mg, 0.065 mmol) in 0.7 mL acetic acid was stirred at 180°C for 10 minutes in microwave. The solvents were removed under reduced pressure. The residue was dissolved in 50 mL of ethyl acetate and was washed with *sat.* aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by preparative TLC sheet (methylene chloride : methanol = 10 : 1) to give a colorless solid (4.6 mg, 22%)
HPLC (4 minute gradient) $t_R$ = 2.31 min; MS m/z 380 (M+H).

## Example 17

3'-Acetylamino-4'-benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide



To a solution of the 3'-Amino-4'-benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide from Example 14 (21 mg, 0.057 mmol) and triethyl amine (29 mg, 0.284 mmol) in 1.5 mL methylene chloride was added acetic anhydride (8.7 mg, 0.085 mmol) at room temperature. The reaction mixture was stirred at that temperature for 6 hours. The mixture was diluted with 50 mL of ethyl acetate and was washed with *sat.* aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by preparative TLC sheet (ethyl acetate : hexanes = 1 : 1) to give a colorless solid (20

mg, 85%).
HPLC (4 minute gradient) $t_R$ = 2.27 min; MS m/z 413 (M+H).

The ability of the compounds of the present invention to inhibit the synthesis or the activity of cytokines can be demonstrated using the following *in vitro* assays.

## Biological Assays

### Generation of p38 kinases

cDNAs of human p38α and β were cloned by PCR. The α and β cDNAs were subcloned into DEST2 plasmid (Gateway, InVitrogen). $His_6$-p38 fusion protein was expressed in *E. coli* and purified from bacterial lysates by affinity chromatography using $Ni^{+2}$-NTA-agarose. $His_6$-p38 protein was activated by incubating with constitutively active MKK6. Active p38 was separated from MKK6 by affinity chromatography. Constitutively active MKK6 was generated in a manner similar to Raingeaud *et al.* [*Mol. Cell. Biol.*, 1247-1255 (1996)].

### TNF-α Production by LPS-Stimulated PBMCs

Heparinized human whole blood was obtained from healthy volunteers. Peripheral blood mononuclear cells (PBMCs) were purified from human whole blood by Accu-paque density gradient centrifugation and resuspended at a concentration of 5 x $10^6$/ml in assay medium (RPMI medium containing 10% fetal bovine serum). 175 uL of cell suspension was incubated with 10 uL of test compound (in 4% DMSO) in 96-well tissue culture plates for 30 minutes at RT. 15 uL of LPS (13.33 ug/ml stock) was then added to the cell suspension and the plate was incubated for 18 hours at 37°C in a humidified atmosphere containing 5% $CO_2$. Following incubation, the culture medium was collected and stored at -20°C.

THP-1 cells (TIB-202, ATCC) were washed and resuspended at a concentration of 1 x $10^5$/ml in assay medium (RPMI medium containing 3% fetal bovine serum). 175 uL of cell suspension was incubated with 10 uL of test compound

(in 4% DMSO) in 96-well tissue culture plates for 30 minutes at RT. 15 uL of LPS (13.33 ug/ml stock) was then added to the cell suspension and the plate was incubated for 18 hours at 37°C in a humidified atmosphere containing 5% $CO_2$. Following incubation, the culture medium was collected and stored at -20°C.

TNF-α concentration in the medium was quantified using a standard ELISA kit (BioSource International, Camarillo, CA). Concentrations of TNF-α and $IC_{50}$ values for test compounds (concentration of compound that inhibited LPS-stimulated TNF-α production by 50%) were calculated by four parameter logistic curve (SigmaPlot, SPSS, Inc.).

**p38α Assay**

The p38α assay employed is based on measurement of ADP released in the reaction of interest through NADH oxidation obtained by coupling with pyruvate kinase and lactate dehydrogenase reactions. The assays were performed in 384-well UV-plates. The final volume was 25 uL prepared from the addition of 2.5 uL compound dissolved in 10% DMSO, 17.5 uL of assay buffer and 5 uL of ATP. Assay buffer contains the following reagents to give final concentration in the assay: 25 mM HEPES, 20 mM 2-glycerophosphate, pH 7.6, 10 mM $MgCl_2$, 0.1 mM sodium orthovanadate, 0.5 mM phosphoenolpyruvate, 0.12 mM NADH, 3.1 mg/ml LDH, 6.67 mg/ml pyruvate kinase, 0.25 mM peptide substrate, 2 mM DTT, 0.005% Tween 80 and 20 nM p38α kinase from Upstate. Test compounds are preincubated with p38α kinase for 60 min and the reaction started by addition of ATP to 0.15 mM final concentration. Reaction rates were measured at 340 nm using SpectraMax plate-reading spectrophotometer for 10 min at 37°C. Inhibition data were analyzed by non-linear least-squares regression using SigmaPlot.

The pharmacological results obtained in the above tests for products indicated in examples in the present application are given in the Table 1 below, the degrees of activites of the products being indicated by + signs according to the ranges of activity indicated in the table, i.e.:

+ for an activity greater than 10 micromolar

++ for an activity of between 1 and 10 micromolar

+++ for an activity of less than 1 micromolar

Table 1

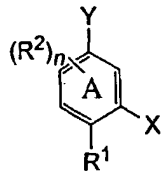
| Example No. | Activity (p-38)<br>+ $IC_{50}$ > 10 μM<br>++ $IC_{50}$ 1- 10 μM<br>+++ $IC_{50}$ < 1 μM | Example No. | Activity (p-38)<br>+ $IC_{50}$ > 10 μM<br>++ $IC_{50}$ 1- 10 μM<br>+++ $IC_{50}$ < 1 μM |
|---|---|---|---|
| 1 | +++ | 11 | +++ |
| 2 | +++ | 12 | +++ |
| 3 | +++ | 13 | +++ |
| 4 | +++ | 14 | +++ |
| 5 | +++ | 15 | +++ |
| 6 | +++ | 16 | +++ |
| 7 | +++ | 17 | +++ |
| 8 | +++ | | |
| 9 | +++ | | |
| 10 | +++ | | |

**TNF-α Production by LPS-Stimulated Mice**

Mice (Balb/c female, 6-8 weeks of age, Taconic Labs; n=8/treatment group) were injected intraperitoneally with lipopolysaccharide (LPS) (50 ug/kg of *E. coli* strain 0111:B4, Sigma) suspended in sterile saline. Ninety minutes later, mice were sedated by $CO_2$:$O_2$ inhalation and a blood sample was obtained. Serum was separated and analyzed for TNF-α concentrations by commercial ELISA assay per the manufacturer's instructions (BioSource International). Test compounds were administered orally at various times before LPS injection. The compounds were dosed either as suspensions or as solutions in various vehicles or solubilizing agents.

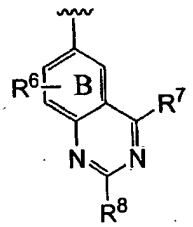
**We claim:**

1. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound having the formula (I):



I

or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein X is



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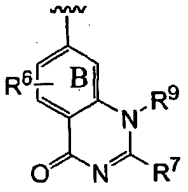

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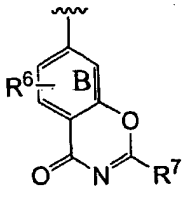

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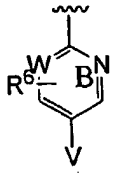
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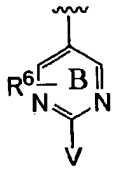
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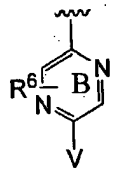
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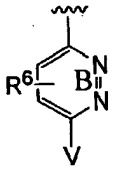
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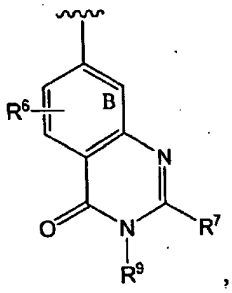
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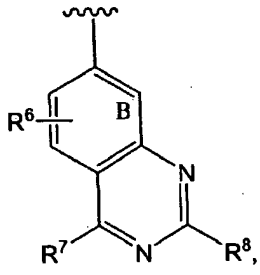
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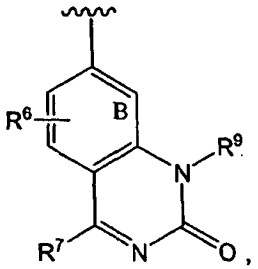
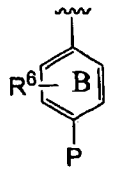




;

$R^1$ is selected from hydrogen, methyl, halogen, hydroxyl, lower alkyl, lower cycloalkyl, alkynyl, trifluoromethyl, methoxy, trifluoromethoxy, cyano, $-NH_2$, $-NR^4R^5$ and $-OR^4$;

$R^2$ is attached to any available carbon atom of the phenyl ring A and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NMe_2$; $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2$-aryl-$R^4$, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, $-S(O)$alkyl, $-S(O)$aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

$R^3$ is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

n is 0 or 1;

t is selected from 0, 1, 2 and 3;

e is selected from 0, 1, 2 and 3;

W is CH or N;

V is $-M-R^{10}$ or $R^{14}$;

M is $-C(=O)NR^4-$, $-NR^4(C=O)-$, $-NR^4(C=O)NR^4-$, $-NR^4SO_2-$, $-C(=O)-$;

$R^{14}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

P is –Q-$R^{10}$ or $R^{15}$;

Q is -$NR^4$ (C=O)-, -$NR^4$ (C=O)$NR^4$-, -$SO_2NR^4$-, -$NR^4SO_2$-, -C(=O)-;

$R^{15}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

Y is –L-$R^3$ or $R^{11}$;

L is –C(=O)NH-,-NH(C=O)-, -$SO_2$NH-, -$NHSO_2$-, -C(=O)-;

$R^{11}$ is an optionally substituted 5-membered heteroaryl;

$R^4$ and $R^5$ are each selected independently from hydrogen, lower alkyl and lower cycloalkyl;

$R^6$ is attached to any available carbon atom of the phenyl ring B and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NH_2$, $-NMe_2$; -S(=O)alkyl, -S(=O)aryl, -$NHSO_2$-aryl-$R^4$, -$NHSO_2$alkyl, -$CO_2R^4$, $-CONH_2$, -$SO_3H$, -S(O)alkyl, -S(O)aryl, -$SO_2NHR^4$, -$NHC(=O)R^4$, and –$NHC(=O)NHR^4$;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl;

$R^9$ is hydrogen, alkyl, substituted alkyl, cycloalkyl;

$R^{10}$ is alkyl, substituted alkyl, aryl, and -$(CH_2)_t$-D-$(CH_2)_e$-$R^{13}$;

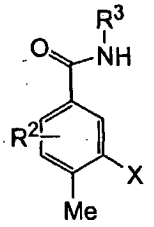
D is selected from a bond, an optionally substituted heterocycle, an optionally substituted aryl, -O-, -S-, -(C=O)-, -$NR^4$(C=O)-, -(C=O)$NR^4$-, -S(O)-, $SO_2NR^4$-, $SO_2$-, and -$NR^4$-

$R^{12}$ is selected from $R^{10}$, $NO_2$, CN, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NMe_2$; -S(=O)alkyl, -S(=O)aryl, -$NHSO_2$-aryl-$R^4$, -$NHSO_2$alkyl, -$CO_2R^4$, $-CONH_2$, -$SO_3H$, -S(O)alkyl, -S(O)aryl, -$SO_2NHR^4$,

and –NHC(=O)NHR$^4$;

R$^{13}$ is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring.

2. A compound having the formula (II) wherein:



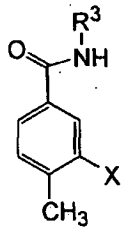

II

R$^2$ is selected from hydrogen, methyl and halogen;

R$^3$ is selected from alkyl, -OR$^4$, substituted alkyl, cycloalkyl, heteroaryl, substituted heteroaryl; and

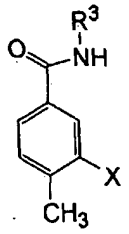
X is selected as in claim 1.

3. A compound of claim 2 having the formula (III).




III

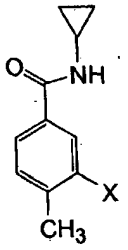
4. A compound of claim 2 having the formula (IV) wherein



IV

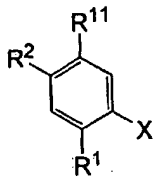
$R^3$ is selected from lower alkyl, lower cycloalkyl, heteroaryl, substituted heteroaryl.

5. A compound of claim 1 having the formula (V).



V

6. A compound of claim 1 having the formula (VI) wherein:

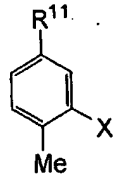


VI

$R^1$ is selected from methyl, cyclopropyl and halogen;

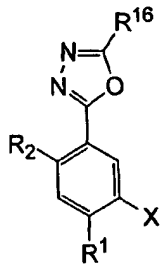
$R^2$ is selected from hydrogen, methyl and halogen.

7. A compound of claim 1 having the formula (VII).



VII

8. A compound of claim 1 having the formula (VIII) wherein:



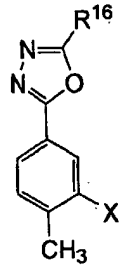
VIII

$R^1$ is selected from methyl, cyclopropyl and halogen;

$R^2$ is selected from hydrogen, methyl and halogen;

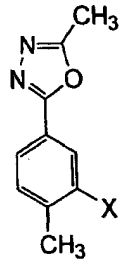
$R^{16}$ is selected from hydrogen, lower alkyl and lower cycloalkyl.

9. A compound of claim 7 having the formula (IX).



IX

10. A compound of claim 1 having the formula (X).



VI

11. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound

according to claim 2.

12. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound according to claim 3.

13. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound according to claim 4.

14. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound according to claim 5.

15. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound according to claim 6.

16. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound according to claim 7.

17. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound according to claim 8.

18. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound according to claim 9.

19. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound

according to claim 10.

20. A method in accordance with claim 1 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

21. A method in accordance with claim 11 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

22. A method in accordance with claim 12 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

23. A method in accordance with claim 13 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

24. A method in accordance with claim 14 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

25. A method in accordance with claim 15 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

26. A method in accordance with claim 16 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis,

septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

27. A method in accordance with claim 17 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

28. A method in accordance with claim 18 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

29. A method in accordance with claim 19 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory

disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

30. A compound of claim 2 selected from:

6-Methyl-4'-[1,3,4]oxadiazol-2-yl-biphenyl-3-carboxylic acid cyclopropylamide;

6-Methyl-4'-(5-methyl-[1,3,4]oxadiazol-2-yl)-biphenyl-3-carboxylic acid cyclopropylamide;

6-Methyl-4'-(4H-[1,2,4]triazol-3-yl)-biphenyl-3-carboxylic acid cyclopropylamide;

*N*-Cyclopropyl-4-methyl-3-(5-[1,3,4]oxadiazol-2-yl-pyridin-2-yl)-benzamide;

*N*-Cyclopropyl-4-methyl-3-[5-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-benzamide;

3-(3-Benzyl-4-oxo-3,4-dihydro-quinazolin-7-yl)-N-cyclopropyl-4-methyl-benzamide;

N-Cyclopropyl-3-[3-(2,6-dichloro-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide;

N-Cyclopropyl-3-[3-(3,4-dichloro-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide;

N-Cyclopropyl-3-[3-(4-methoxy-benzyl)-4-oxo-3,4-dihydro-quinazolin-7-yl]-4-methyl-benzamide;

N-Cyclopropyl-4-methyl-3-(4-oxo-3,4-dihydro-quinazolin-7-yl)-benzamide;

4'-Benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide;

6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-(4-methoxy-benzyl)-nicotinamide;

*N*-(4-Methoxybenzyl)-2-[(5-cyclopropylaminocarbonyl)-2-methylphenyl]-4-aminopyrimidine-5-carboxyamide;

3'-Amino-4'-benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide;

*N*-Cyclopropyl-4-methyl-3-(2-oxo-4-phenyl-1,2-dihydro-quinazolin-7-yl)-benzamide;

*N*-Cyclopropyl-4-methyl-3-(4-phenyl-quinazolin-7-yl)-benzamide; and

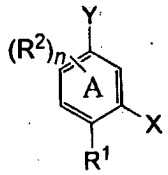
3'-Acetylamino-4'-benzoyl-6-methyl-biphenyl-3-carboxylic acid cyclopropylamide.

31. A method of treating one or more conditions associated with p38 kinase activity

comprising administering to a patient in need thereof at least one compound according to claim 30.

32. A method in accordance with claim 31 wherein the cytokine-mediated disease is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft vs. host disease, allograft rejection, fever, myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome(AIDS), AIDS related complex, (ARC), keloid formation, scar tissue formation, Crohn's diosease, ulcerative colitis or pyresis.

33. A method of inhibiting p38 kinases, comprising contacting a p38 kinase with compound having the formula (I):



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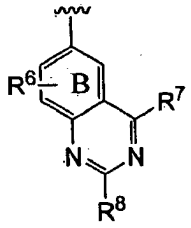
or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein X is



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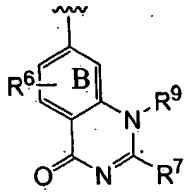

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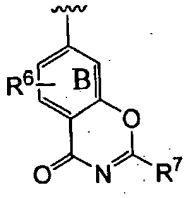

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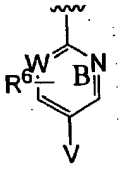

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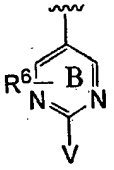

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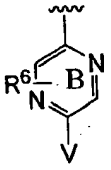

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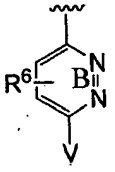

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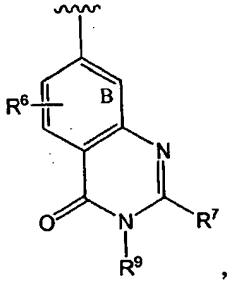

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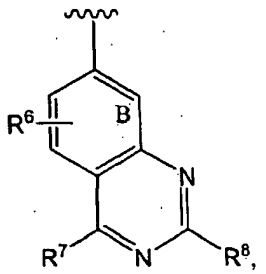

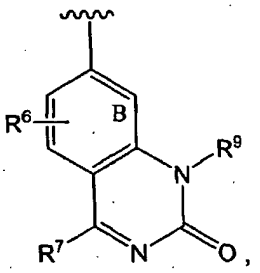

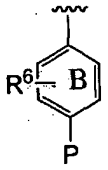

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$R^1$ is selected from hydrogen, methyl, halogen, hydroxyl, lower alkyl, lower cycloalkyl, alkynyl, trifluoromethyl, methoxy, trifluoromethoxy, cyano, $-NH_2$, $-NR^4R^5$ and $-OR^4$;

$R^2$ is attached to any available carbon atom of the phenyl ring A and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NMe_2$; $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2$-aryl-$R^4$, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, $-S(O)$alkyl, $-S(O)$aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

$R^3$ is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

n is 0 or 1;

t is selected from 0, 1, 2 and 3;

e is selected from 0, 1, 2 and 3;

W is CH or N;

V is –M-$R^{10}$ or $R^{14}$;

M is –C(=O)$NR^4$-,-$NR^4$(C=O)-,-$NR^4$(C=O)$NR^4$-, -$NR^4SO_2$-, -C(=O)-;

$R^{14}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

P is –Q-$R^{10}$ or $R^{15}$;

Q is -$NR^4$ (C=O)-, -$NR^4$ (C=O)$NR^4$-, -$SO_2NR^4$-, -$NR^4SO_2$-, -C(=O)-;

$R^{15}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

Y is –L-$R^3$ or $R^{11}$;

L is –C(=O)NH-,-NH(C=O)-, -$SO_2$NH-, -$NHSO_2$-, -C(=O)-;

$R^{11}$ is an optionally substituted 5-membered heteroaryl;

$R^4$ and $R^5$ are each selected independently from hydrogen, lower alkyl and lower cycloalkyl;

$R^6$ is attached to any available carbon atom of the phenyl ring B and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, -$NH_2$, -$NMe_2$; -S(=O)alkyl, -S(=O)aryl, -$NHSO_2$-aryl-$R^4$, -$NHSO_2$alkyl, -$CO_2R^4$, -$CONH_2$, -$SO_3H$, -S(O)alkyl, -S(O)aryl, -$SO_2NHR^4$, -NHC(=O)$R^4$, and –NHC(=O)$NHR^4$;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl;

$R^9$ is hydrogen, alkyl, substituted alkyl, cycloalkyl;

$R^{10}$ is alkyl, substituted alkyl, aryl, and -$(CH_2)_t$-D-$(CH_2)_e$-$R^{13}$;

D is selected from a bond, an optionally substituted heterocycle, an optionally

substituted aryl, -O-, -S-, -(C=O)-, -$NR^4$(C=O)-, -(C=O)$NR^4$-, -S(O)-, $SO_2NR^4$-, $SO_2$-, and -$NR^4$-

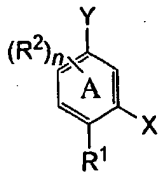
$R^{12}$ is selected from $R^{10}$, $NO_2$, CN, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, -$NMe_2$; -S(=O)alkyl, -S(=O)aryl, -$NHSO_2$-aryl-$R^4$, -$NHSO_2$alkyl, -$CO_2R^4$, -$CONH_2$, -$SO_3H$, -S(O)alkyl, -S(O)aryl, -$SO_2NHR^4$, and –NHC(=O)$NHR^4$;

$R^{13}$ is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring.

34. The method of claim 33, wherein the compound is a compound of any of claims 2-10 and 30.

35. The method of claim 33 or claim 34, wherein the p38 kinase is p38α or p38β kinases.

36. A method of mediating cytokine response, comprising administering to a subject in need thereof an effective amount of compound having the formula (I):

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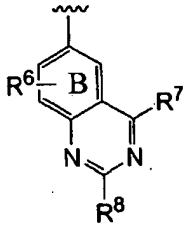
or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein X is



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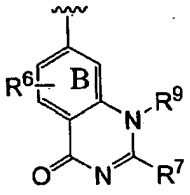

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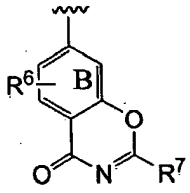

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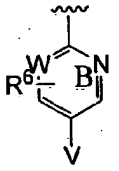

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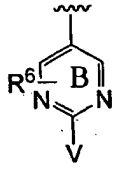

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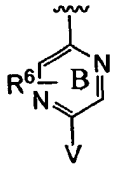

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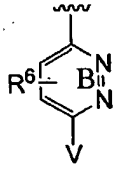

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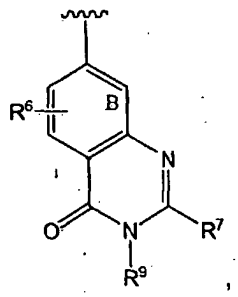


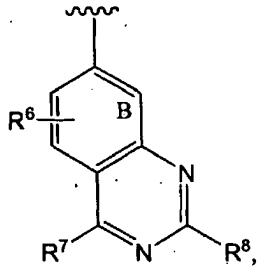


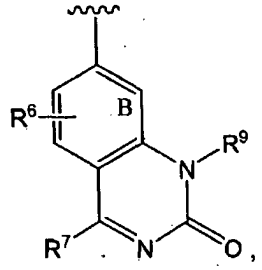


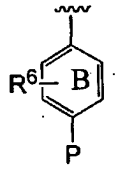


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$R^1$ is selected from hydrogen, methyl, halogen, hydroxyl, lower alkyl, lower cycloalkyl, alkynyl, trifluoromethyl, methoxy, trifluoromethoxy, cyano, $-NH_2$, $-NR^4R^5$ and $-OR^4$;

$R^2$ is attached to any available carbon atom of the phenyl ring A and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NMe_2$; $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2$-aryl-$R^4$, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

$R^3$ is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted

heterocycle;

n is 0 or 1;

t is selected from 0, 1, 2 and 3;

e is selected from 0, 1, 2 and 3;

W is CH or N;

V is –M-$R^{10}$ or $R^{14}$;

M is –C(=O)$NR^4$-,-$NR^4$(C=O)-, -$NR^4$(C=O)$NR^4$-, -$NR^4SO_2$-, -C(=O)-;

$R^{14}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

P is –Q-$R^{10}$ or $R^{15}$;

Q is -$NR^4$ (C=O)-, -$NR^4$ (C=O)$NR^4$-, -$SO_2NR^4$-, -$NR^4SO_2$-, -C(=O)-;

$R^{15}$ is aryl or heteroaryl optionally substituted with up to three $R^{12}$;

Y is –L-$R^3$ or $R^{11}$;

L is –C(=O)NH-,-NH(C=O)-, -$SO_2$NH-, -$NHSO_2$-, -C(=O)-;

$R^{11}$ is an optionally substituted 5-membered heteroaryl;

$R^4$ and $R^5$ are each selected independently from hydrogen, lower alkyl and lower cycloalkyl;

$R^6$ is attached to any available carbon atom of the phenyl ring B and at each occurrence is independently selected from hydrogen, alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, -$NH_2$, -$NMe_2$; -S(=O)alkyl, -S(=O)aryl, -$NHSO_2$-aryl-$R^4$, -$NHSO_2$alkyl, -$CO_2R^4$, -$CONH_2$, -$SO_3H$, -S(O)alkyl, -S(O)aryl, -$SO_2NHR^4$, -$NHC(=O)R^4$, and –$NHC(=O)NHR^4$;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, substituted

alkyl, aryl, cycloalkyl;

$R^9$ is hydrogen, alkyl, substituted alkyl, cycloalkyl;

$R^{10}$ is alkyl, substituted alkyl, aryl, and $-(CH_2)_t-D-(CH_2)_e-R^{13}$;

D is selected from a bond, an optionally substituted heterocycle, an optionally substituted aryl, -O-, -S-, -(C=O)-, $-NR^4(C=O)-$, $-(C=O)NR^4-$, -S(O)-, $SO_2NR^4-$, $SO_2-$, and $-NR^4-$

$R^{12}$ is selected from $R^{10}$, $NO_2$, CN, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, -OMe, -CN, $-NMe_2$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-aryl-$R^4$, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

$R^{13}$ is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring.

37. The method of claim 36, wherein the compound is a compound of any of claims 2-10 and 30.

## ABSTRACT

Compounds and compositions for modulating the activity of p38 kinases are provided, including p38α and p38β kinase. Methods for treating, preventing or ameliorating one or more symptoms of a p38 kinase mediated disease or disorder are also provided.

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Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse